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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JULY, 1948

## ORIGINAL ARTICLES

### ELECTROLYTE CHANGES IN NEPHROSIS

OCCURRENCE OF DIURESIS FOLLOWING ADMINISTRATION OF SODIUM AND  
POTASSIUM SALTS\*

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THE child with nephrotic edema has an excessive volume of extracellular fluid. The chemical composition of his plasma, a small fraction of the total extracellular fluid, is abnormal in that its albumin concentration is markedly reduced. It is a less familiar fact that the chemical composition of the entire extracellular fluid is also abnormal. Thus the concentrations of both sodium and bicarbonate are reduced and that of chloride is increased. The cause of these abnormal concentrations is unknown at present but it is pertinent to ask what effects they might produce.

The decrease in plasma albumin is generally assumed to permit increased amounts of an ultrafiltrate of plasma to pass from the vascular bed into the tissue spaces. Thus hypoproteinemia is commonly thought to be responsible for the edema. However, it has been observed repeatedly that loss of edema

can occur without elevation of plasma protein, which may remain pathologically low for weeks or months after edema has been lost through diuresis. In contrast, the reduction in plasma sodium makes it possible for water to migrate from the extracellular compartment into the cells of the body, causing intracellular edema. The lowered plasma bicarbonate and elevated chloride are characteristic of chronic acidosis which also produces a shift of water into tissue cells.<sup>11,22,29</sup>

Shifts of extracellular water have important secondary effects. Thus transfer of extracellular water into cells (as in the Darrow-Yannet experiment<sup>6,13</sup> or after sodium depletion in man<sup>17</sup>) reduces the plasma volume. Reduction of plasma volume by sodium depletion<sup>13</sup> has been shown to result in decreased glomerular filtration and delayed excretion of water.<sup>12,17</sup> Although

\* This paper was read at a meeting of the Society for Pediatric Research at Stockbridge, Massachusetts, on May 12, 1947.

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renal function studies in nephrosis have resulted in both super and sub-normal clearances,<sup>7</sup> the studies of Oliver<sup>20</sup> indicate the need for considerable caution in interpreting such measurements. Certainly the clearance of water and sodium is not increased. The effects of intracellular edema on the

i. e., lactate or the more rapidly convertible acetate) might produce two important results: (1) elevate the concentration of sodium in extracellular fluid and the concentration of bicarbonate in both extracellular and intracellular fluids; (2) move water out of cells thereby further expanding both

TABLE 1.—TYPICAL PLASMA AND URINE ELECTROLYTE CONCENTRATIONS IN NEPHROSIS  
(All concentrations are expressed in mEq. per liter)

	Na	HCO <sub>3</sub>	Cl	K	HPO <sub>4</sub>	H
Plasma . . . .	132	14	108	5	2	0 0001
Urine . . . .	10	0 01	10	180	70	0 01
U/P ratio . . .	0 1	0 001	0 1	36	35	100
<i>Normal Values</i>						
Plasma . . . .	142	27	103	5	2	0 0001
Urine . . . .	140	10	100	50	20	0 001
U/P ratio . . .	1	0 3	1	10	10	10

function of organs, such as the kidney, can only be surmised at present. In any event, reduced plasma volume might interfere with nutrition of cells; this added to the chronic acidosis and intracellular edema, would presumably augment the loss of potassium from body cells. These may also have suffered intrinsic damage from the disease itself.

If these suppositions are true, the composition of the urine should reflect these disturbances. The urine would be scanty in volume, acidic in reaction, and low in sodium but high in potassium. These inferences are consistently fulfilled while edema persists, thereby attesting the kidneys' ability to protect homeostasis as far as possible in this difficult situation. Average values found in all children we have observed, together with normal values, are summarized in Table 1. Similar plasma values have previously been noted<sup>1,2,4,11</sup> but not correlated with the edema and oliguria.

In view of these chemical abnormalities, it seemed reasonable to anticipate that administration of sodium bicarbonate (in the form of its precursors,

plasma and extracellular volumes. Certain changes in kidney function would then follow: the *filtration of sodium* would increase markedly. Furthermore, as shown by Pitts,<sup>25</sup> when the excretion of bicarbonate at high plasma levels is greatly increased in association with accelerated urine flow, chloride reabsorption is decreased and chloride is excreted in the urine. Apparently the capacity of the tubules to reabsorb chloride can be reduced by presenting to them simultaneously an excess of bicarbonate. Excretion of chloride is desired as a means of removing extracellular fluid.

The administration of potassium would presumably permit its replacement in cells as the total osmotic pressure (not that of the colloids alone) of extracellular fluid was increased by sodium administration. In view of the osmotic equilibrium between the potassium concentration inside the cells and the sodium concentration of the surrounding medium,<sup>11,22</sup> the intracellular concentration of potassium cannot be raised to normal until the extracellular concentration of sodium is likewise raised to normal. Thus administra-

tion of potassium only has not proven effective although excess potassium promotes water excretion.<sup>30</sup> Excess bicarbonate formed from potassium acetate would further augment bicarbonate excretion and thereby add to the strain on the chloride reabsorptive mechanism.

Finally, the introduction of considerable alkaline electrolyte into the tubular urine might inhibit precipitation of protein in the renal tubules, as suggested by the *in vitro* experiments of Oliver.<sup>19</sup>

**Methods:** Sodium and potassium in plasma and urine were determined by the lithium internal standard flame photometer,<sup>3</sup>

the use of which for biological fluids has been described.<sup>9</sup> In R. W., plasma sodium was determined by a gravimetric uranyl zinc acetate method after dry ashing. Chlorides were determined by the method of Schales and Schales;<sup>27</sup> alkaline urines were brought to the correct pH for titration by one or two drops of 3 per cent nitric acid. The other analyses were performed by the hospital laboratories using standard methods.

**Procedure and Observations:** Observations have been made in children with massive edema and ascites, hypoproteinemia (A/G ratio less than one) and marked proteinuria but without hyperazotemia. The urine contained small numbers of red cells and occasional granular casts; hypertension was absent or minimal; lipemia was marked. The presumptive diagnosis in these children

TABLE 2.—SUMMARY OF BALANCES OF SODIUM, CHLORIDE AND POTASSIUM  
(All data are for 30 day periods of observation)

Patient	Age	Body weight (kg.)			Na	Cl	K
		Initial	Final	Loss	(Total milliequivalents in 30 days)		
<i>Diuresis Following Administration of Sodium Lactate (1 Molar Solution)</i>							
R. W.	7	43.9	25	18.9			
Recovered in urine (42.4 l.)					—9080	—3943	—1153
Recovered in 4.8 l. ascitic + 0.7 l. pleural fluid					—800	—605	—28
Intake of sodium lactate					+6750		
Diet (estimated) + penicillin infusion—1.8 l.					+1170	+1170	+900
Balance					—1960	—3378	—281
Weight loss × concentration in E.C.F.					+2640	+1980	+95
Net					+680*	—1398*	—186
<i>Spontaneous Diuresis</i>							
G. B.	8½	46.3	31.7	14.6			
Recovered in urine					—5400	—5500	—1250
Diet (estimated)§§					+1200	+1200	+1200
Balance					—4200	—4300	—50
Weight loss × concentration in E.C.F.					+2050	+1530	+75
Net					—2150	—2770†	+25
<i>Diuresis Following Administration of Sodium and Potassium Acetate</i>							
R. P.	3½	24	18	6			
Recovered in urine					—7300	—2455	—3600
Medicinal intake					+8000‡		+4000
Diet (estimated)§§					+900	+900	+900
Balance					+1600	—1555	+1300
Weight loss × concentration in E.C.F.					+840	+660	+30
Net					+2440‡	—895	+1330

\* Sodium and chloride continued to be excreted in the urine in considerable quantity above their intake for remaining 8 days of hospitalization. Inclusion of these amounts would balance the sodium column and increase the excess chloride excretion.

† Although this total may seem excessive, the urine chloride concentration frequently ranged from 200 to 254 mEq. per liter during chloruresis; (See Fig. 2).

‡ These values may be too high because some sodium was lost by vomiting and error in sodium dosage initially. There was also considerable excess sodium excretion in the week following this 30-day collection period; some lag in sodium excretion follows administration of large amounts.

§§ Diet low in Na. and Cl. only partially consumed because of anorexia and emphasis on Na. and K medication intake.

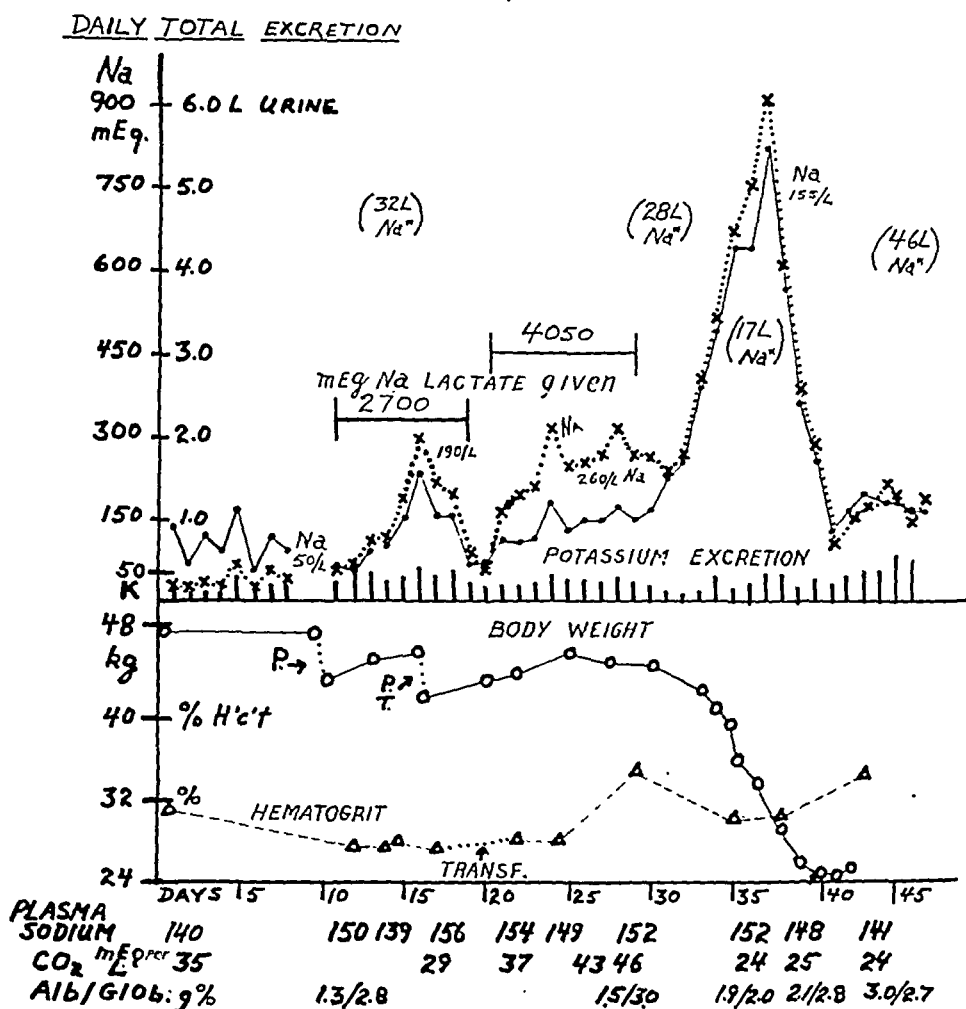


FIG. 1.—Changes after giving sodium lactate, 1 molar 400 cc, daily, and the effect of sodium lactate administration on nephrosis with massive anasarca. (RW 7 years.) The volume of urine (solid line) and its content of sodium (dotted line with crosses) are plotted on the vertical axis with the scales adjusted so that 1000 cc. of urine corresponds with 150 mEq. of sodium. This facilitates recognition of changes in urine composition, e. g., when the sodium concentration in the urine is 150 mEq. per liter, the points for urine volume and total sodium coincide; when the concentration of sodium in the urine is greater than 150 mEq. per liter, the point for total sodium falls above the point for volume and vice versa for dilute urine. Representative values are printed on the chart. The amount of sodium lactate administered in the interval between the vertical lines is printed over a horizontal line placed at a level on the sodium scale which corresponds to the average daily sodium intake. The values in parenthesis are the liters of sodium space (12) represented by the apparent volume of distribution of radi sodium 15 hours after injection.

The daily potassium excretion is shown by the height of the vertical lines; 50 mEq. of K is marked on the ordinate. Body weight is plotted below; at the vertical arrows and capital P, 7 and 4.8 liters of ascitic fluid and 0.7 liter of pleural fluid were moved. The hematocrit values are plotted to indicate relative changes in blood volume.

At the bottom of the chart are plasma values of sodium and bicarbonate in mEq. per liter and for albumin and globulin in grams per 100 cc. of plasma; the A/G ratios were below unity.

During the first 10 days of observation, small volumes of acid urine low in Na were obtained. Sodium lactate was then given cautiously; plasma Na increased and the concentration of Na in the urine rose rapidly to 210 mEq. per liter (day 15); urine volume tripled. Then the plasma Na decreased (day 13) suggesting a movement of water from cells into extracellular fluid. Continuation of sodium administration and excretion of more water than sodium in the urine raised plasma Na to 156 mEq. per liter (day 17). When sodium administration was interrupted, both the volume of urine and its concentration of Na decreased promptly. With further sodium administration, the volume of urine rose only slightly but the concentration of Na increased sharply to 274 mEq. per liter (day 27). Although lactate was not given after the 29th day, the plasma Na remained over 150 mEq. per liter; urine Na decreased to this level and the urine chloride increased from 15 to 25 mEq. per liter to equal and then exceed (142 mEq. per liter) the plasma chloride as the daily volume of urine rose to a maximum of 5.5 liters on the 36th day.

The change in the appearance and behavior of the child was dramatic as the massive edema and anasarca rapidly disappeared and the body weight was halved. Just prior to diuresis, the potassium concentration of the urine dropped sharply to 7.7 mEq. per liter (day 31) and remained in this range for 10 days. In the subsequent days, electrolyte values in plasma and urine became normal. The protein content of the urine fluctuated from 1.9 to 4.3 gm. per day. No additional therapy was given and the child was discharged edema-free. It was of further interest that the hematocrit of 31% decreased to 27% with sodium administration and then rose to 35% after diuresis. The proteins decreased from 4.1 to 3.85 gm. per 100 cc. prior to diuresis. These values suggest expansion of plasma and extracellular volumes prior to diuresis with subsequent decrease toward normal.

was either lipid nephrosis or the nephrotic phase of glomerulonephritis.

The first child studied had remained edematous for 15 weeks. He received sodium lactate as a one molar (six times isotonic) solution by mouth. Fluids were moderately restricted but not to the point of marked thirst. The sequence of events, summarized in Figure 1, was as follows: The volume of urine and the concentration of urinary sodium increased. The plasma sodium rose, then fell, apparently as a result of movement of water from cells to the extracellular compartment. With additional intake of sodium,

per liter to that of the plasma and above. Urine sodium decreased from 270 mEq. per liter to 155, equalling plasma concentration. Thus the urine being excreted required minimal osmotic work on the part of the kidney.<sup>18</sup> At this point, four days after the last dose of sodium lactate, the volume of urine increased by a liter per day to reach 5.5 liters daily and the sodium and chloride concentrations remained approximately equiosmotic with the plasma.

During this period edema and ascites disappeared; body weight and extracellular volume returned to normal. Plasma proteins re-

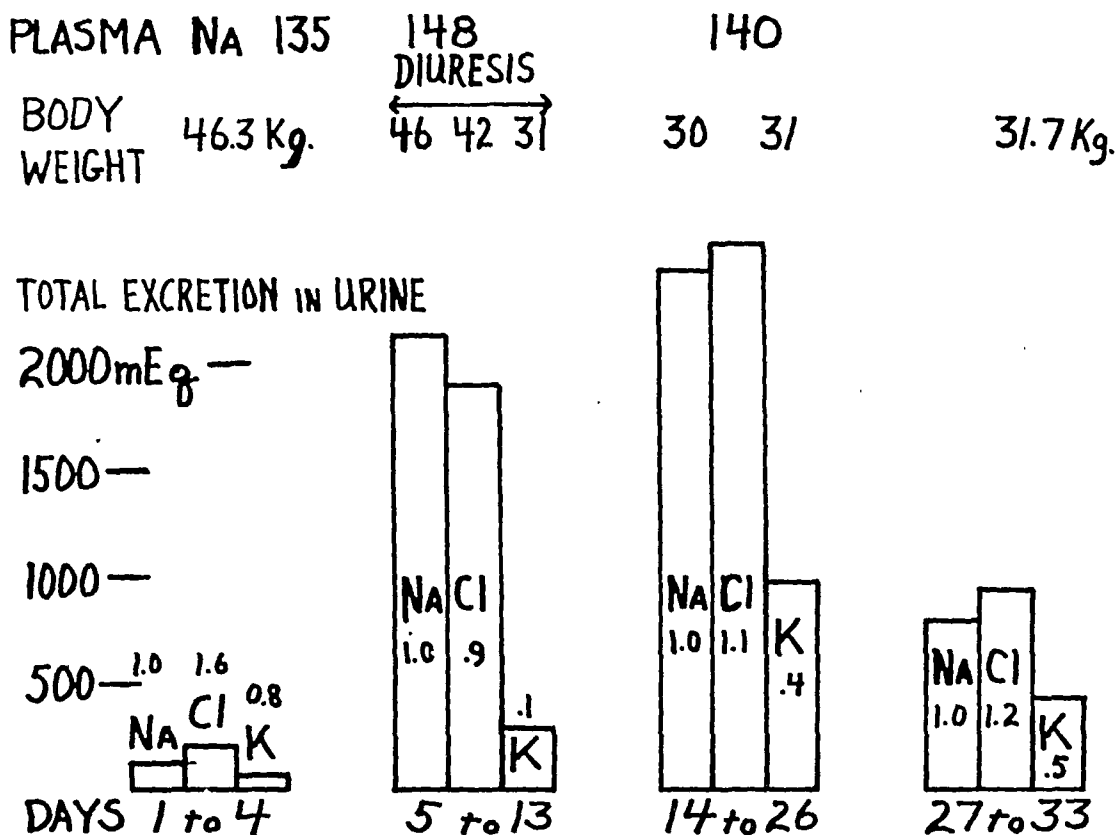


FIG. 2.—Electrolyte excretion in spontaneous diuresis. Urine Na increases to equi-osmoticity with the plasma as plasma Na increased from 135 to 148 mEq. per liter and urine volume increased 5-fold. Chloride excretion rose sharply; body weight decreased. After the 12th day no further decrease in body weight occurred; nevertheless, excretion of Na, Cl and K continued at high levels for over 2 weeks. The average mEq. excreted per diem of Na, Cl and K respectively in each period are days 1 to 4:—29, 48, 23. Days 5 to 13:—236, 211, 31. Days 14 to 26:—186, 196, 67. Days 27 to 33:—109, 131, 59. The ratios of the excretion of Cl and K to Na taken as 1.0 are placed above the symbols in each box.

plasma sodium increased to over 150 mEq per liter and remained elevated. The plasma bicarbonate increased slowly; in contrast, urine bicarbonate increased rapidly, values above 300 mEq. per liter having been observed.

The apparent extracellular volume, ( $\text{Na}^+$ ) in Figure 1, as measured by radiosodium<sup>15</sup> decreased slightly, as did body weight.

After seven days, with urine sodium and bicarbonate in excess of 250 mEq. per liter, chloride reabsorption apparently failed; urine chloride suddenly rose from under 15 mEq.

maintained virtually unchanged during the 40-day period except for a decrease from 4.5 to 3.9 gm. per 100 cc. at the peak of diuresis.

The total amount of sodium excreted represents the sum of the sodium administered plus the amount derived from the volume of edema fluid removed. In contrast, the overall balance sheet in this child, and also in all others similarly studied (Table 2), brings to light an enormous store of chloride

which was jettisoned in excess of that expected from the volume of edema fluid. The site of the excess chloride is not known; the cells are suspected and, indeed, the erythrocytes of all children measured showed increased chlorides ranging up to twice the normal value. The shift of chloride into red cells has been studied by Van Slyke<sup>29</sup> and Peters<sup>23</sup> and is rather characteristic of acidosis, the presence of which was inferred at the outset from the persistently lowered plasma bicarbonate. (See Figure 4). The exact degree of acidosis needs to be established by measurement of pH. Furthermore, the excess chloride is only partially accounted for by increased concentra-

tions in the red cells. Obviously, analyses of other tissues is required to settle this point.

The frequent occurrence of spontaneous diuresis in this syndrome provided an opportunity to study such an episode in another patient. The total electrolyte excretion and the ratio of potassium and chloride to sodium in the urine, together with the changes in body weight, are shown in Figure 2. During the period of maximal edema there was a relatively high potassium excretion. This has been a consistent finding. It strongly indicates intracellular derangement and suggests the need for potassium administration. It is also worthy of note that the chloride

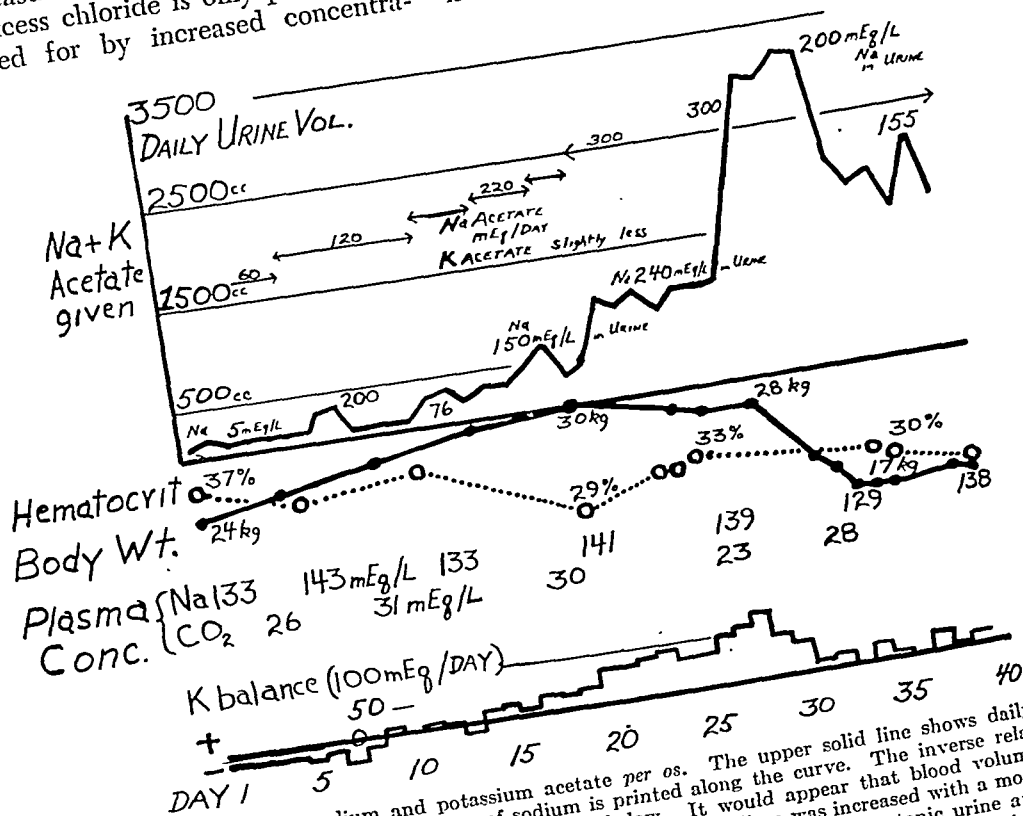


FIG. 3.—Changes after sodium and potassium acetate per os. The upper solid line shows daily urine volume and its average concentration of sodium is printed along the curve. The inverse relationship of body weight and hematocrit are indicated below. It would appear that blood volume increased with Na and K administration prior to diuresis. Plasma sodium was increased with a moderate increase in plasma bicarbonate. Diuresis in this instance occurred with hypertonic urine and consequently plasma sodium was carried below normal, then returned to normal. The potassium balance (not including diet) is indicated; retention of 980 mEq. occurred from the 17th to 30th day inclusive. This is considerably in excess of a reasonable allowance for potassium in the food consumed during this 2 week period of anorexia associated with the large intake of not especially palatable medication.

excretion considerably exceeded the sodium output. After having been edematous for nine weeks, during a few days of observation in this hospital without any attempt at treatment a minor crysipeloid infection occurred, plasma sodium rose from 135 to 148 mEq. per liter and the urine composition suddenly approached that of extracellular fluid. For the next few days the U/P ratio of sodium and chloride approached unity and urine of a concentration representing minimal renal osmotic work<sup>18</sup> was excreted in increasing volume as ascites and edema disappeared and body weight decreased to normal. Then followed a period of strikingly greater sodium and chloride excretion *but no weight loss*. Inasmuch as potassium excretion increased sharply at this time, it would appear that the normally extracellular sodium and chloride, together with potassium, left the intracellular compartment. The overall balance sheet (Table 2) shows a rather large excess excretion of chloride, similar to that mentioned above, after the induced diuresis. In relation to the weight of edema and ascitic fluid lost, the sodium excretion was twice that expected; the chloride excretion, however, was three times that expected. There was also considerable potassium excretion at certain intervals. These shifts of electrolytes without water focused our attention on the intracellular compartment, the site of enzyme activities, in searching for an explanation of this syndrome. In any event, increase of intracellular pH from below normal, by elevation of the pH of extracellular fluid and shift of additional bicarbonate into cells with restoration of Donnan's equilibrium between cells and extracellular fluid, could account for this removal of electrolytes (chiefly chloride) from cells. In this connection, the experiments of Rapoport and Guest<sup>26</sup> and Peters<sup>23</sup> have indicated the type of

changes that might occur in cells with changes of their pH.

During the past six months, the interest of Dr. Murray Bass and the cooperation of Dr. Jerome Kohn and Dr. Ralph Moloshok at Mt. Sinai Hospital have afforded additional opportunities of profiting by earlier experience.

The schedule of dosages carried out by Dr. Moloshok and the measurements made in our laboratory are shown in Figure 3, which contains observations on a third patient. This child had been edematous for nine weeks and there was an additional period of observation for basal values. Then sodium acetate therapy was begun but potassium administration deferred (although plasma potassium was below normal) because the urine volume was scanty. Plasma and urine sodium both rose, urine volume increased and there was a gain in weight of 5 kg. in 16 days. Sodium and potassium acetate were pushed; whereupon the hematocrit decreased, suggesting an increase in plasma volume; the urine sodium and bicarbonate fell toward normal; retention of potassium occurred; urine chloride rose from 15 mEq. per liter to the level of plasma chloride. With urine electrolytes nearly equiosmotic with the plasma, the volume of urine rose sharply and body weight decreased as ascites and edema disappeared. The balance sheet here (Table 2) is more complicated, but again the chloride excreted greatly exceeded the amount anticipated from the volume of edema lost. Although dietary intake was not measured precisely, there seems to have been potassium retention.

The question of alkalosis always arises. Figure 4, from Gamble's monograph,<sup>11</sup> helps explain why it has not caused tetany, except in one patient classified as chronic nephritis; doubling plasma bicarbonate requires only a small increase of carbonic acid to prevent an undesirable rise in plasma pH. When the medication is increased gradually, urinary excretion of bicarbonate rises to over 300 mEq. per liter and its output almost parallels intake. Large amounts of sodium bicarbonate and sodium lactate have been administered to patients with acidosis associated with extensive thermal burns,<sup>8</sup> with renal obstruction from sulfona-

mides,<sup>14</sup> and to prevent renal obstruction during massive sulfadiazine therapy.<sup>10</sup> Alkalosis did not occur in these instances and urinary output increased markedly.

**Discussion:** It is important to emphasize that this study is presented as an experimental approach to the problem of nephrotic edema. More cases are needed to distinguish between

therapeutic effect and spontaneous diuresis. To date, diuresis has occurred in 14 children after administration of these salts sufficient to raise plasma sodium to 140 mEq. per liter or over and urine sodium to 200 mEq. per liter or over; a detailed report will be published shortly. In the presence of marked signs of renal damage, changes in plasma sodium and bicarbonate con-

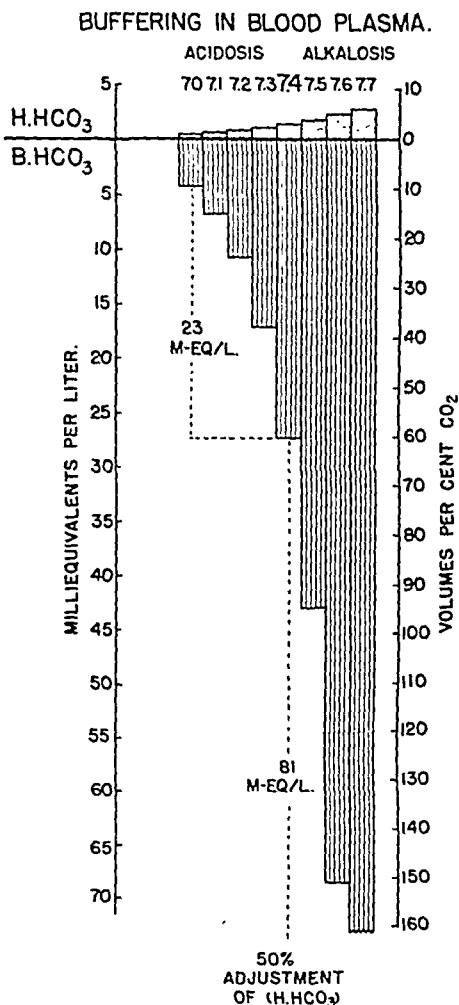


FIG. 4.—Buffering in blood plasma. (From Gamble.) Plasma pH is adjusted by the ratio of H<sub>2</sub>CO<sub>3</sub> (above the zero line) to B.HCO<sub>3</sub> (below the zero line). The normal ratio is 3/60. Consequently, relatively huge increases in B.HCO<sub>3</sub> cause but slight change in pH when a small and easily accomplished increase in H<sub>2</sub>CO<sub>3</sub> follows. In this diagram 50% adjustment by H<sub>2</sub>CO<sub>3</sub> is shown; only small increases in pH occur with very large increases in B.HCO<sub>3</sub>.

It is doubtful if plasma pH exceeded 7.5 since plasma CO<sub>2</sub> values in excess of 95 volumes % were seen only once and that child showed no manifestations of alkalosis with a CO<sub>2</sub> of 120 volumes %.

Nevertheless, tetany occurred in 2 patients with poor renal function and should be watched for and guarded against. Inhalation of 10% CO<sub>2</sub> and 90% oxygen gave prompt relief.

centration may occur more rapidly, hence dehydration and tetany need to be guarded against by frequent plasma analyses.

More time is needed to evaluate the effects of sustained electrolyte administration on the signs of renal damage: hypertension, azotemia, casts, red and white cells as well as the massive proteinuria. One three-year-old child has been observed for 28 months, subsequent to diuresis following administration of sodium lactate. During this period sodium and potassium medication has been continued and up to the time of writing the child has remained clinically well, free of edema and without protein or abnormal urinary sediment. Other children receiving medication 6 to 8 months after diuresis have remained edema-free but without subsidence of proteinuria. (The intake of sodium and potassium acetate is adjusted to obtain approximately 140 mEq. per liter of Na and 100 mEq. per liter of K in the pooled 24-hour urine. From 5 to 15 grams of each salt per day have been required.) In our very meagre experience, children kept on maintenance therapy have remained free of edema longer than those not so maintained. Obviously, study of many patients for a period of years is necessary for final evaluation. Preliminary studies by Osman<sup>21</sup> and Schultz<sup>28</sup> did not indicate any increase in life expectancy with somewhat similar management but the factors of renal osmotic work,<sup>18</sup> inhibition of protein pre-

cipitation in the tubular urine,<sup>19</sup> chronic acidosis, reduced plasma sodium concentration and potassium replacement have not been studied heretofore.

The great excess of chloride recovered in the urine after diuresis needs careful study. It appears to be greater in those children who subsequently have the longest remissions. Complete metabolic balance studies are essential; in their absence, calculated intakes together with urine chlorides 1.5 to 2.0 times the plasma concentration indicate excess excretion. A dry storage of chloride has been suggested previously<sup>5</sup> and some lipoid-chloride has been described.<sup>24</sup> Furthermore, the *in vivo* experiments of Wilde<sup>30</sup> demonstrate the presence of chloride in *muscle fibers* and also delineate a shift of chloride and potassium into muscle fibers as the sodium content of the extracellular fluid is lowered and its potassium increased. Complete potassium balances are also essential to establish the retention indicated by the present data.

**Summary.** Significant abnormalities in the concentration of electrolytes in plasma and urine in children with nephrotic edema are described. Diuresis occurred following administration of sodium lactate and sodium and potassium acetate. The electrolyte changes during these episodes and in the course of spontaneous diuresis are presented.

We are indebted to Miss Betty B. Freeman for her painstaking care in performing the electrolyte analyses and for her patience in carrying out numerous comparative gravimetric analyses to establish the accuracy of the lithium internal standard flame photometer.<sup>3,9</sup>

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# VASCULAR OCCLUSION AND ISCHEMIC INFARCTION IN SICKLE CELL DISEASE\*

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FROM the accumulated reports of clinical and postmortem observations of cases of sickle cell disease the following concept of its pathology has been formed. The abnormal shape of the sickled erythrocyte is responsible for the stasis of blood flow in capillaries, resulting in thrombosis and subsequent infarction. The principles of this concept, with added modifications, have been accepted by most writers.

We had the opportunity to observe a case of uncomplicated sickle cell disease which revealed multiple foci of ischemic necrosis of inner organs without thrombotic occlusion of arteries. In view of the seeming rarity of such a finding, we believe it to be justified to put this case on record. Also from a review of the literature we have gained the impression that interpretations from repeated and transmitted quotations have outgrown the reported facts. We have attempted, therefore, an analysis of previous reports with particular reference to vascular occlusions in sickle cell disease and its relation to ischemic infarction.

**Summary of Case History.** Pleasant S., an 11 year old colored female, was admitted to the Poliomyelitis Unit of the Charlotte Memorial Hospital because of weakness and hypo-esthesia of the extremities which had steadily been increasing for the preceding 4 weeks. She complained of moderate abdominal distress.

The left extremities were more affected than those of the right. The child stated that she had recurrent episodes of right upper abdominal distress of approximately 4 to 7 days duration. These symptoms regressed spontaneously but were followed by a period of extreme weakness. During these periods the mother noted slightly icteric sclerae.

On admission the child complained of pain in the left extremities. Temperature was 100° F., pulse 90, respiration 20. She was poorly nourished and appeared lethargic. The left extremities could not be moved voluntarily. There was no icterus at this time. Moderate rigidity was demonstrable in the right epigastric and right hypochondriac regions of the abdomen, with severe tenderness in the right upper quadrant and in the midclavicular line. A mass was definitely palpable at this point, measuring approximately 5 cm. in diameter. It seemed to be attached to the inferior surface of the liver. Direct and rebound tenderness were referred to this area. Peristaltic sounds were markedly diminished in frequency and volume.

**Neurologic Examination.** The reflexes were slightly hyperactive on the right and definitely hyperactive on the left where pathologic reflexes were elicited with ease. Abdominal reflexes were diminished in all 4 quadrants. There was increased tonicity with diminution of muscular power in the left extremities. Position and vibratory sensations were intact.

**Laboratory Examination on Admission.** White blood cells, 26,000 per c.mm. (neutrophils, 91%); red blood cells, 3,210,000; hemoglobin (Sahli), 6-gm. (41%). Two days prior to admission there were 15,000 white blood cells per c.mm. and 3,800,000 red blood cells; hemoglobin (Sahli), 52%. Blood Wassermann and Kahn were negative. Examination of spinal fluid (2 days prior to admission) revealed a markedly increased pressure with 10 cells per c.mm. No further information was available. Urine: albumin 1+ with occasional red blood cells and white blood cells, as well as occasional granular casts.

**Clinical Course.** The temperature gradually increased, as did the abdominal symptoms. The patient was placed upon a penicillin regimen. A flat Roentgen ray plate

\* The author is indebted to the Heineman Foundation for the illustrations used in this paper.

of the abdomen revealed numerous calculi in the area of the gall bladder. A tentative diagnosis of acute cholecystitis was made. Laparotomy was performed 1 day after admission. During operation a friable necrotic gall bladder was removed. A blood sample was taken on the day of operation for determination of active or latent sickling and "97% active sickling" was reported 12 hours after operation. The condition of the patient became increasingly poor. Icteric sclerae were noted 8 hours postoperatively. She expired in hyperpyrexia 48 hours postoperatively.

*Autopsy.* (1 hour 30 minutes after death.)

*Lungs:* There were extensive areas of atelectasis and bronchopneumonia in both lungs. No vascular changes (including thrombosis) were found on gross or microscopic examination. *Spleen:* The spleen was grossly not definitely recognizable. In its place was found an ill-defined area of thickening at the inferior surface of the diaphragm which measured approximately 2 x 2 x 0.5 cm. It was very firm in consistency and appeared to consist of a tough whitish capsule containing small dark red vascular areas. Microscopically, this portion of tissue consisted of extremely thickened, hyalinized trabeculae containing residual vessels with marked calcification. Hematoidin crystals were closely intermingled with calcium deposit. A few residual sinusoids filled with red blood were encountered. Lymph follicles proper were not identified. *Kidneys:* The entire cortex of both kidneys was mottled by numerous yellowish gray, sharply demarcated foci of rhomboid or wedge-shaped configuration. Many of them were confluent. Most of them did not involve more than the outer 1 cm. of the cortex and were slightly elevated over the surface as well as the cut surface. The cortical architecture of the renal parenchyma within these foci was completely obscured. The dissectable blood-vessels were patent throughout. Microscopically, the above-described areas were typical of ischemic necroses with margins of neutrophil infiltration. Platelet thrombi were found in some glomerular tufts and occasionally in capillaries and arterioles within the infarcted zones but no thrombi and no endothelial proliferation were noted elsewhere. Within the normal portions of the parenchyma the capillaries, particularly those of the glomeru-

lar tufts, were markedly engorged with red blood cells. *Gall bladder:* (Surgically removed.) Revealed almost complete necrosis of all layers of its wall without inflammatory reaction. It contained 8 faceted bilirubin cholesterol-calcium stones. No vascular occlusion was demonstrated. *Liver:* The consistency was somewhat friable. Many sharply demarcated areas were noted in the right lobe. They were rhomboid in shape, yellowish in color on the cut surface, with completely obscured architecture. Many of them were surrounded by a narrow hemorrhagic zone. The dissectable vessels were patent throughout. Microscopically, scattered large foci of coagulation necrosis were found, mostly in the center of liver lobules. These were surrounded by zones of neutrophilic infiltration which were followed by zones of marked hyperemia. The liver cells in the better preserved portion were filled with coarsely granular bile pigment. Vascular changes, particularly thromboses, were not noted. *Brain:* The gyri were slightly flattened and the sulci narrowed. Numerous foci of degeneration were found, characterized by depression of white matter, in both hemispheres. These foci were light grayish yellow in color and softer than the normal-appearing white matter in some portions and firmer in others. They were sharply demarcated and irregular in shape and size, the largest measuring 4 cm., involving almost the entire white matter of the left posterior temporal lobe, anterior parietal lobe, and encroaching somewhat upon the internal capsule. Other foci, including the posterior portion of the corpus callosum, were observed. The gray matter appeared mainly involved, as were the basal ganglia. Microscopically, numerous, often closely packed, large foam cells were found within the areas of demyelination of the white matter. The myelin sheaths had completely disappeared and a network of delicate glial fibers had remained. In most of the larger foci the axon cylinders were also completely disintegrated. In some areas, particularly in the corpus callosum, marked glial scarring in the vicinity of foci of demyelination could be demonstrated. Occasional accumulations of red cells were encountered in perivascular lymph spaces and some of the sections showed considerable accumulations of small round cells, as well as some foam cells, in the Virchow-Robin lymph spaces. Some



FIG. 1.—*Kidney*. Ischemic infarction with extended area of incomplete ischemic necrosis (A) in which some preserved glomeruli can be observed

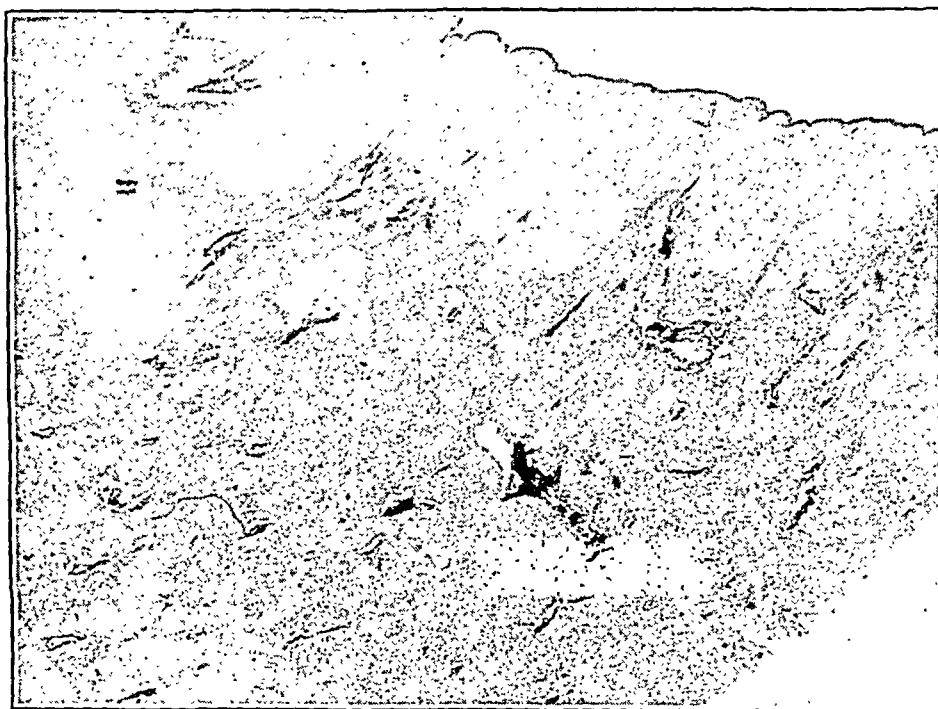


FIG. 2.—*Liver*. Low power magnification shows extensive subcapsular ischemic necrosis.

iron pigmented macrophages were also found.

In none of the vessels, small or large, was there found thrombotic occlusion or endothelial proliferation. Fat could not be demonstrated in capillary lumina.

**SUMMARY OF CASE.** An 11 year old colored girl who was admitted to the

hospital with the suspected diagnosis of poliomyelitis went into sickle cell crisis. Because of the clinical picture of "acute surgical abdomen" and the presence of gall stones, the gall bladder was removed. Death occurred 2 days later. The post-mortem examination revealed diffuse bi-

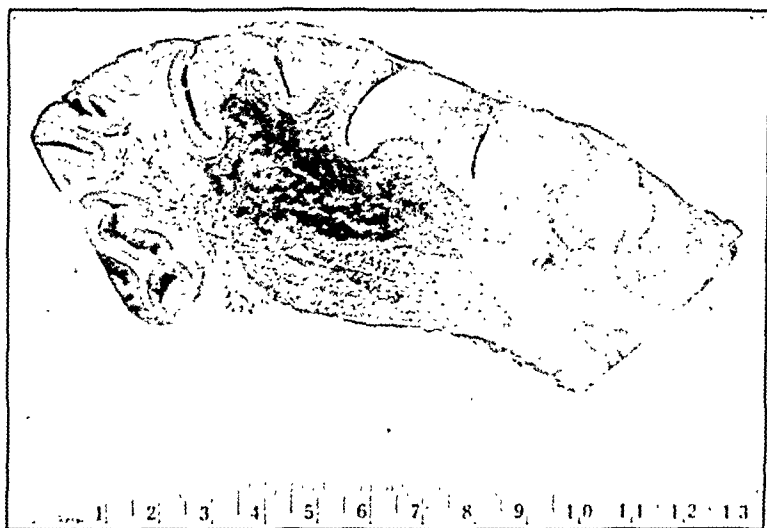


FIG. 3.—Cerebral cortex shows large area of softening in white matter.  
(Nigrosin Stain, according to R. C. Beck<sup>2</sup>)



FIG. 4.—Brain. Marked perivascular round cell infiltration within areas of ischemic softening.

lateral cortical necroses of the kidney, diffuse ischemic infarctions of the liver, ischemic necrosis of gall bladder and multiple large foci of necrosis in the brain. Sick cells and engorgement of capillaries were prominent but vascular thrombosis was absent. The only condition to which all of the clinical symptoms and pathologic changes could be attributed was the presence of marked sickling of red blood cells and anemia.

**Discussion.** As indicated in the introduction, we found it difficult to reconcile the morphologic findings in this case with the current consensus, according to which the ischemic infarctions are attributable to capillary blockade followed by arterial thrombosis.

*Capillary engorgement* has often been described as a prominent finding. Diggs and Ching,<sup>6</sup> in particular, have drawn our attention to this phenomenon and it has

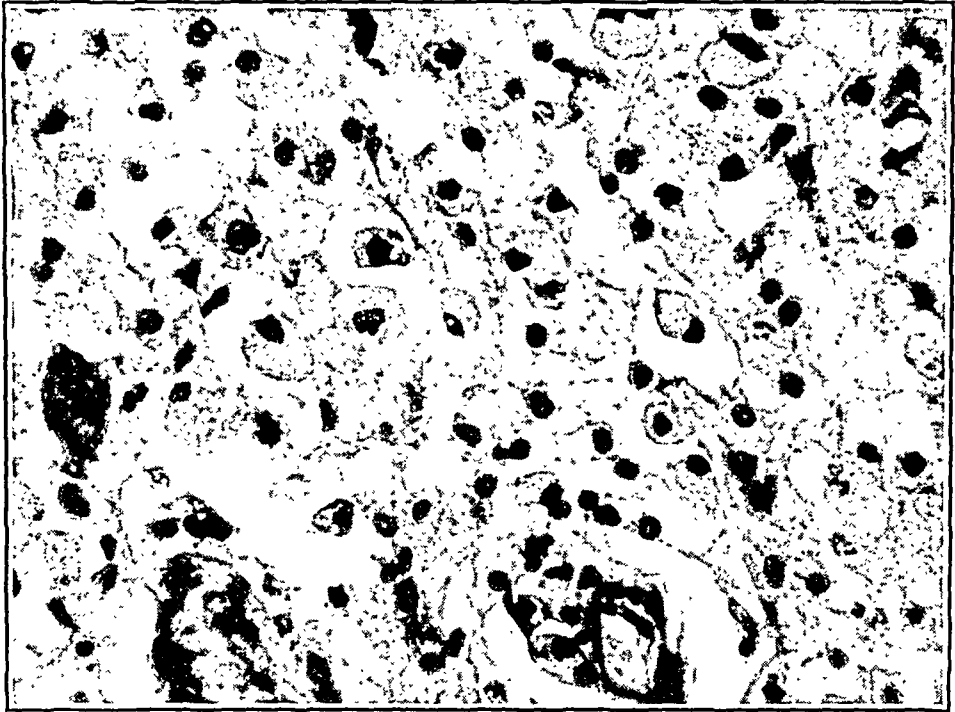


FIG. 5. *Brain.* Accumulation of "foam cells" within area of ischemic softening.

been concluded that the odd-shaped, rigid erythrocytes block the capillaries. This process is supposed to initiate capillary stasis which in turn is followed by thrombosis (Murphy and Shapiro,<sup>14</sup> Bauer<sup>1</sup>). Our case, likewise, shows marked capillary engorgement and areas are encountered where the packing of red blood cells resembles conglutination.

An interpretation of these microscopic observations, in our opinion, must take into consideration the fact that capillary stasis, for the most part, is transitory in nature. Only exceptionally are true capillary thrombi formed. It is hard to reconcile the transitory character of the stasis with a mechanical blocking of the capillaries by sickled cells.

Reestablishment of capillary flow may conceivably come about by disintegration of red blood cells. Bauer<sup>1</sup> postulates such disintegration resulting from "conglutination." If the reestablishment of circulation, however, were due to massive disintegration of red blood cells in all of the static capillaries, we would expect evidence of intravascular hemolysis. This has not been demonstrated. It has been pointed out that hemoglobinuria is absent (Haden<sup>10</sup>), and destruction of red blood

cells is, therefore, believed to take place in the reticuloendothelial system.

As long as the red blood cells are "packed," they cannot obtain sufficient oxygen to regain their spherical shape and elasticity. It is, therefore, obvious that the rigid sickled cell, unless destroyed, must pass as such through the bottle-neck when the crisis recedes. This can only be explained by widening of the capillary bed or increase of peripheral blood pressure. Hence, it is our opinion that the engorgement of capillaries does not result from purely mechanical block by sickled cells. We assume that functional changes of the peripheral vascular apparatus are the cause of stasis as well as reestablishment of blood flow.

*Arterial thrombosis* does not fully account for the ischemic necroses of inner organs. Our own observation appears to be ample proof that other factors than mechanical occlusion may be responsible for this change. Thrombi, particularly in cerebral vessels, undoubtedly occur in cases of uncomplicated sickle cell disease but not as consistently as one is led to believe.

If one disregards the numerous statements of arterial thrombosis merely based on partially correct and partially errone-

ous quotations, the actual occurrence appears to be limited to a relatively small number of cases. In fact, we have only been able to find definite evidence of thrombosis in the cerebral vessels in 4 cases (Hughes, Diggs and Gillespie;<sup>12</sup> Connel;<sup>5</sup> Tomlinson;<sup>18</sup> Bridgers<sup>4</sup>). Frequent reference is also made to thrombi in lungs, spleen and other inner organs.

In checking such references as are available we have not been able to find convincing evidence. Wertham, Mitchell and Angrist<sup>21</sup> reported pulmonary infarctions and thrombosis (Case 1) but do not exclude its embolic origin. In their second case, pulmonary infarctions were found histologically but thrombosis was not mentioned. Mallory<sup>13</sup>, reported numerous pulmonary infarctions in a case of sickle cell disease, complicated by sepsis and rheumatic fever. He stressed the fact that thrombi could hardly be found outside the infarcted regions proper. We infer that these thrombi were probably secondary to the tissue necrosis rather than their cause.

Infarcts in the spleen, according to Diggs and Ching,<sup>6</sup> are common but they add that no thrombi in arteries or veins are noted. "Smaller arterioles," however, show endarteritis and thrombosis. These, in our opinion, do not account for grossly noticeable infarctions. Wertham, Mitchell and Angrist,<sup>21</sup> for instance, reported an isolated recent infarct in the spleen with a mural thrombus in an arteriole which was included in the area of infarction. Wade and Stevenson<sup>19</sup> spoke of areas of "pale staining necroses" in the spleen but reported no thrombi. Bridgers<sup>4</sup> (Case 2) described a large splenic infarction without being able to demonstrate thrombi grossly or microscopically. Hein and Thorne<sup>11</sup> spoke of areas in the spleen which were grossly suspected to be infarctions but which upon histologic examination failed to reveal necrosis. On the other hand, Bennett<sup>3</sup> reported thrombosis in small and medium-sized arteries in the spleen but no infarctions.

Infarctions in the liver or, at least, foci of necrosis have been mentioned (Ben-

nett<sup>3</sup>) but thromboses of hepatic arteries, to our knowledge, have not been recorded. Yater and Mollari<sup>23</sup> described in detail a clot in the hepatic artery but admitted that it was probably formed after death. Thrombi in renal arteries are, likewise, not described, though scars in the cortex are frequently referred to as healing infarctions (Graham,<sup>9</sup> and others) without evidence of thrombosis. We have not been able to find reference to thrombi in arteries of other organs though they are frequently mentioned in general statements.

Thus, the search for arterial thrombi in sickle cell disease yielded surprisingly few conclusive reports, particularly when one takes into account the efforts which have been made to explain their pathogenesis.

Stasis (due to capillary blockade and vasodilatation), endothelial damage (due to anoxia), and an increase of coagulating bodies in the circulating blood have been held responsible for the supposedly frequent occurrence of vascular thrombosis in sickle cell disease. The existence of capillary stasis cannot be questioned. Capillary thromboses may also occur, although in many reports in which they have been specifically mentioned, they have been seen within areas of necroses. The description of such thrombi is often inconclusive, and Wertham, Mitchell and Angrist<sup>21</sup> stated that many of them, in their cases, were probably agonal. Most authors imply that the thrombi result directly from stasis, although our present knowledge of the pathogenesis of thrombosis requires additional precipitating factors. Murphy and Shapiro<sup>14</sup> refer to the experimental work of Pennell<sup>16</sup> who demonstrated that disintegration of platelets is the result of their conglutination with red blood cells. Pennell, however, in his experiments and conclusions referred to "shed blood." We still have no evidence that intravascular stagnation of blood flow alone without endothelial damage or changes in the coagulating properties of the blood leads to thrombosis.

Capillary thromboses at any rate are of relatively minor importance inasmuch as their occurrence is not consistent and inasmuch as they cannot bring about the massive foci of necroses in brain, spleen, kidney and liver, which are being discussed. In order to explain these, thrombi in respectively large arteries must be demonstrated or vascular spasm may be assumed.

As pointed out before, ischemic infarctions have been described more often without than with related thrombi. Furthermore, cases of sickle cell disease have been put on record and have been quoted, in which associated renal disease and hypertension may have been responsible for the vascular lesion (Wertham, Mitchell and Angrist;<sup>21</sup> Hughes, Diggs and Gillespie<sup>12</sup> 'Case 2'). On the other hand, absence of thrombi in large vessels corresponding to the ischemic infarctions have been repeatedly stated (Hughes, Diggs and Gillespie;<sup>12</sup> Wade and Stevenson;<sup>19</sup> Bridgers;<sup>4</sup> and our own case). It can, therefore, be concluded that ischemic infarctions may occur in sickle cell disease with, and perhaps more often without, thrombotic occlusion of arteries.

The cause of thrombosis of large arteries, if it occurs, has, as yet, not been satisfactorily explained. Murphy and Shapiro<sup>14</sup> assume that stasis leading to thrombosis causes liberation of coagulating bodies into the circulation, thus accounting for thrombosis of larger vessels. Their own observations, however, regarding the prothrombin time in their case of sickle cell crisis show prolonged prothrombin time, heralding the approach of crisis, returning to "slightly below normal." It appears to us that these limited findings do not constitute a safe basis on which arterial thromboses can be explained.

In the absence of thrombotic vascular occlusion, fat emboli have been thought of as playing a part in bringing about parenchymatous necroses. Wade and Stevenson,<sup>19</sup> and Wertham, Mitchell and Angrist<sup>21</sup> did not find changes in the bone marrow. The significance of so-called fat

emboli remains questionable. In the first place, Wertham, Mitchell and Angrist<sup>21</sup> did not find them consistently correlated to the foci of necrosis in the brain and, in the second place, they would hardly account for large wedge-shaped infarctions. In our case, we were unable to find fat in the capillaries of the brain.

Finally, *endarteritis* has repeatedly been described and postulated as the primary cause of parenchymatous damage. Endothelial proliferation with or without hyalinization of arteriolar walls has been observed several times in the brain and occasionally in the spleen. Bridgers<sup>4</sup> noted obliterating endarteritis in the brain of 1 of his cases; Yater and Hansmann<sup>22</sup> report obliterating thromboangiitis of the lung with hypertrophy of the right heart in 1 case. The findings of true obliterating endarteritis cannot be regarded as an essential pathologic feature in sickle cell disease since they have been observed only exceptionally. In view of the relative frequency of sickle cell disease in the colored race and the extreme rarity of true endarteritis, the correlation appears to be coincidental rather than causative.

**Comment.** If we confine ourselves to such pathologic observations that have been consistently reported in cases of uncomplicated sickle cell disease, we find that little has been added since the presentation of this subject by Diggs and Ching<sup>6</sup> in 1934. The many varieties of morphologic changes, however, are still not satisfactorily correlated. One group of phenomena revolving around the hemolytic anemia includes the siderofibrosis of the spleen, hemosiderosis of liver and kidneys (Stasney<sup>17</sup>), the relative frequency of gall stones (Weens<sup>20</sup>), the hematologic changes in the peripheral blood as well as in the bone marrow. The initial enlargement of the spleen and its subsequent atrophy and fibrosis may also belong to this group, although the pathogenesis of this process is not clearly understood.

The second group of phenomena—to which we shall confine our comments—concerns circulatory disturbances. Ische-



mic necroses of inner organs, though frequently observed, are not consistently found. They may or they may not be associated with organic changes in the vascular tree. Degenerative changes in the vessel walls, endarteritis, thrombosis, and fat emboli have been described. The greatest handicap in the evaluation of these findings lies in the still relatively limited number of postmortem examinations. Not all of the previous reports permit a clear concept of the relationship between the vascular lesions and the sickle cell disease. It has been repeatedly suspected that coincidental diseases might actually have been the cause of vascular changes.

In an attempt to correlate most of these phenomena we are inclined to fall back on our own observations, from which we have learned that extensive ischemic infarctions may occur in uncomplicated cases of sickle cell disease without visible organic changes in the vascular tree. The same set of circumstances is encountered in other conditions. The changes in the liver, in our case, simulate closely those seen in severe eclampsia or in shock following extensive burns (Duffin<sup>8</sup>). Cortical necroses of the kidney have often been described in pregnancy and other apparently unassociated conditions. The isolated infarctions of the spleen, kidney and brain have been described as the result of trauma without mechanical vascular occlusion. Neuburger<sup>15</sup> first pointed out that vascular spasm is apparently responsible for such occurrence. We have repeatedly observed ischemic infarctions of kidneys, spleen, small intestine and brain, in post-traumatic cases in which careful gross and microscopic search appeared to exclude satisfactorily a thrombotic occlusion of the responsible artery.

Duff and Murray<sup>7</sup> have compiled the theories concerning the pathogenesis of bilateral renal necrosis and it appears reasonable to us to apply similar thoughts to the ischemic necroses in sickle cell disease. If we suppose that the process is initiated by vascular spasms, it may be

assumed that vasodilatation may follow and that the stagnation of blood flow may result in ischemic necrosis of vessel walls, with subsequent thromboses. Depending on the duration of the vascular spasm, the blood flow may be reestablished at any one of these stages and ischemic infarctions may thus be found with or without thrombosis, with or without the degenerative changes in the vascular wall. Stasis, however, is most commonly found.

Tomlinson<sup>18</sup> finds the clinical signs and symptoms of sickle cell crisis referable to shock associated with rapid destruction of red blood cells. This proposition dovetails readily into the previously mentioned hypothesis of vascular spasm as the initiating factor leading to parenchymatous necroses.

The clinical record of our own case, as that of many others, shows typical sickle cell crisis but does not indicate an actual state of shock prior to the laparotomy. The laboratory data, however, are not sufficiently complete. The patient was not examined for relative hemoconcentration and the plasma protein level was not determined. Actual shock was precipitated by the operation and it is likely that the blood pressure during the sickle cell crisis was maintained by peripheral vascular spasm, assumed to occur during the pre-shock stage.

The sequence of events, as we see it at this time, presents itself as follows: 1. Accepting Tomlinson's theory as a working hypothesis, the sickle cell crisis constitutes an equivalent to pre-shock or shock. The crisis may be initiated by various factors which produce a decrease of oxygen in the peripheral blood. It is characterized by rapid blood destruction and an obviously mounting diminution of the oxygen-carrying capacity of the red blood cells. The mere fact that the erythrocytes are sickled proves that they do not carry sufficient oxygen. In accordance with our present concept, peripheral vascular spasms may at least temporarily maintain normal blood pressure, but it will also increase tissue anoxia, leading to

further sickling and to the introduction of a vicious cycle.

2. The peripheral vascular spasm may lead directly to ischemic necrosis in inner organs or may be followed by capillary dilatation or stasis. During this phase of failure of peripheral circulation the capillaries are "engorged" and "packed" with sickle cells. We regard this phenomenon as a result rather than the cause of capillary stasis.

3. Local ischemia of tissue and capillary walls may result in organic damage to the vessel walls, degenerative changes, thrombosis, resulting further in superimposed infarctions.

We are presenting this hypothesis as a plausible explanation of the multitude of findings, all of which can be traced directly to various phases of one and the same process. It explains the frequent reports of ischemic infarctions without vascular thrombosis, as well as the occurrence of thrombi. It eliminates the concept of primary capillary blockage which cannot be correlated to gross infarctions without

assuming an unrelated process in larger vessels.

**Summary.** 1. A case of sickle cell disease is reported in which cholecystectomy in sickle cell crisis resulted in death of the patient.

2. Multiple large foci of ischemic necrosis were observed in inner organs. The changes in the brain resembled those of Schilder's encephalitis, those in the liver simulated the changes in eclampsia, those in the kidneys bilateral cortical necrosis.

3. No organic changes in the vascular tree were observed. Thrombi, in particular, were absent.

4. A review of the literature in contrast to the current opinion reveals the inconsistency of vascular changes, thromboses and the lack of correlation between parenchymatous necroses and mechanical vascular occlusions.

5. A theory is presented intending to correlate the multitude of morphologic findings with particular reference to ischemic infarctions of inner organs in sickle cell disease.

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AN EVALUATION OF THENYLENE HYDROCHLORIDE  
[N,N-DIMETHYL-N'-(ALPHA-PYRIDYL)-N'-(ALPHA-THENYL)  
ETHYLENEDIAMINE HYDROCHLORIDE]

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DIPHENHYDRAMINE hydrochloride (benadryl hydrochloride or beta-dimethylaminoethyl benzhydrieth erhy drochloride) and tripelennamine hydrochloride (pyribenzamine hydrochloride) or N,N-dimethyl-N'-benzyl-N'-(alpha-pyridyl) ethylenediamide hydrochloride are now being used extensively as adjuncts to the therapeutic armamentarium in the treatment of dermatoses characterized by pruritus, especially those with cutaneous edema, such as urticaria and angioneurotic edema. Our study was undertaken in order to evaluate thenylene hydrochloride [N',N-dimethyl - N' - (alpha - pyridyl) - N' - (alpha-thenyl) ethylenediamine hydrochloride], a new addition to the group of antihistamine drugs. We wish to record our experience with its therapeutic efficacy in dermatologic conditions, its untoward reactions, and an incidental observation of the relative merits of the 3 drugs, thenylene, benadryl and pyribenzamine.

Thenylene hydrochloride is a white crystalline material possessing antihistamine qualities. It is non-hygroscopic but readily soluble in water. Studies by the originators of the drug (Abbott Laboratories) on isolated portions of the ileums of guinea pigs and intestines of rabbits have shown that thenylene has definite activity in preventing or abolishing spasm produced by histamine. In animals it has a negligible effect on blood pressure when given intravenously in doses of less than 1 mg. per kg. of body weight.

Data on 126 patients treated with thenylene at the Mayo Clinic will be pre-

sented in this report. Thenylene has been used in the treatment of additional patients, but sufficient observations have not been made on them to allow inclusion of this part of our experience in this preliminary report. The 126 patients concerning whom we are reporting had a variety of dermatologic conditions. About 50% were hospitalized during at least part of our observation and about 50% were seen as out-patients only. All of the patients received regular dermatologic care, such as application of soothing lotions, ointments, wet dressings and so forth. This fact renders a statistically valid report impossible, but we have attempted in so far as possible to evaluate the patient's reactions to the antihistamine drugs studied. All of the patients received thenylene; 39 received both benadryl and pyribenzamine in addition to thenylene; 8 received benadryl and thenylene, and 5 received pyribenzamine and thenylene. The dosages used varied but in general benadryl and pyribenzamine were given by mouth in doses of 50 mg. 3 or 4 times a day and thenylene in doses of 100 mg. 3 or 4 times a day. No patient received treatment with more than 1 of these drugs at a time.

The observations are summarized in Tables 1 to 5. The responses have been classed arbitrarily into 3 categories: definite improvement, slight improvement and no improvement. In most cases pruritus was the symptom which responded to treatment. In the cases of urticaria and angioneurotic edema relief or im-

provement was indicated by lessening or abolition of edematous wheals or plaques as well as cessation of the pruritus. In the cases of dermatitis venenata and eczema improvement meant not only partial or complete relief from pruritus but in some cases the drugs seemed to hasten the resolution of vesicular dermatitis. It is not possible to separate the rôle of local and general supportive treatment from that played by the drugs under consideration. In our data many dermatoses were represented, but for the sake of simplicity and because the number of cases in the different categories was for the most part so small, many cases were included in the group called "miscellaneous conditions." The miscellaneous group consisted of cases of dermatitis venenata, exfoliative dermatitis of unknown etiology, mycosis fungoides, dermatitis herpetiformis, subacute disseminated lupus erythematosus, erythema nodosum, secondary sensitization dermatitis due to overtreatment and others.

The data regarding the 126 patients who received thenylene are summarized in Table 1. In all, 86 (68.2%) gained some degree of relief. For certain of the conditions little was anticipated from the use of this drug. For atopic dermatitis the main effect anticipated was some relief from the paroxysms of pruritus which usually accompany this condition. Of the 28 patients who had atopic dermatitis, 18 obtained varying degrees of relief. On the other hand 10 of these patients felt the drug was ineffective in ameliorating the pruritus. It is noteworthy that those who had urticarious lesions, whether acute or chronic, gave the most satisfactory response. In the urticaria and angioneurotic group were cases in which the etiology was known as well as some in which it was unknown. Four out of 5 patients who had anal or vulval pruritus were helped. In the miscellaneous group the best response was obtained in cases of acute dermatitis venenata.

Of the patients, 47 were given benadryl as well as thenylene (Table 2); 33 (70.2%)

were benefited by use of benadryl. Of the 44 patients who received pyribenzamine, 24 (54.5%) were helped (Table 3).

The proportion of patients in the 4 diagnostic categories of Tables 1, 2 and 3 are roughly the same. The tables, therefore, lend themselves to a rough comparison of responses obtained. It should be pointed out that although some patients received all 3 drugs, all did not. The patients were not chosen for this study in any particular way. They were seen by different physicians who had available 3 preparations, thenylene, benadryl and pyribenzamine. The observations are thus those of the patients and the various physicians who frequently prescribed 1 preparation and tried another only if 1 of the others failed to help. Certainly no statistically valid conclusions can be drawn, yet the material is extensive enough to allow clinical observations of the effects of these drugs.

Comparison of the results of use of the 3 drugs revealed that 70.2% of the patients objectively showed or subjectively felt improvement from use of benadryl, 68.2% from use of thenylene, and 54.5% from use of pyribenzamine hydrochloride. The response varied markedly in the different groups by diagnostic classification. In cases of urticaria and angioneurotic edema the objective change following treatment, namely, decrease in size or disappearance of the wheals, could be observed best. Also the condition is definitely one resulting from extravasation of fluid which causes localized edema and thus is directly responsive to antihistamine preparations. As expected, all of the drugs showed the most marked activity in this group. Out of 25 patients, 22 were helped with thenylene, 7 out of 9 with benadryl, and 6 out of 7 with pyribenzamine. Thus in our experience for a condition responding to the direct antihistamine properties of the drugs all 3 were of relatively equal value.

Of 28 patients, who had atopic dermatitis 18 felt that thenylene gave them relief from pruritus, while 12 of 14 and

TABLE 1.—THERAPEUTIC EFFECTIVENESS OF THIENYLENE

Diagnosis	Degree of improvement (cases)			Total cases
	Definite	Slight	None	
Atopic dermatitis . . . . .	11	7	10	28
Eczema* . . . . .	11	17	11	39
Urticaria and angioneurotic edema . . . . .	19	3	3	25
Miscellaneous conditions . . . . .	9	9	16	34
Total . . . . .	50	36	40	126

\* Other than classical atopic dermatitis including: multiple lichen simplex chronicus, nummular eczema, exudative neurodermatitis, and so forth.

TABLE 2.—THERAPEUTIC EFFECTIVENESS OF BENADRYL

Diagnosis	Degree of improvement (cases)			Total cases
	Definite	Slight	None	
Atopic dermatitis . . . . .	7	5	2	14
Eczema* . . . . .	6	4	5	15
Urticaria and angioneurotic edema . . . . .	7	0	2	9
Miscellaneous conditions . . . . .	1	2	6	9
Total . . . . .	21	11	15	47

\* Other than classical atopic dermatitis including: multiple lichen simplex chronicus, nummular eczema, exudative neurodermatitis, and so forth.

TABLE 3.—THERAPEUTIC EFFECTIVENESS OF PYRIBENZAMINE

Diagnosis	Degree of improvement (cases)			Total cases
	Definite	Slight	None	
Atopic dermatitis . . . . .	2	4	6	12
Eczema* . . . . .	4	5	5	14
Urticaria and angioneurotic edema . . . . .	6	0	1	7
Miscellaneous conditions . . . . .	1	2	8	11
Total . . . . .	13	11	20	44

\* Other than classical atopic dermatitis including: multiple lichen simplex chronicus, nummular eczema, exudative neurodermatitis, and so forth.

TABLE 4.—PATIENTS PREFERRING A CERTAIN DRUG

Diagnosis	Thienylene	Benadryl	Pyribenzamine	Total patients	
				With preference	Taking all 3 drugs
Atopic dermatitis . . . . .	2	3	3	8	12
Eczema* . . . . .	3	1	0	4	13
Urticaria and angioneurotic edema . . . . .	4	0	0	4	6
Miscellaneous . . . . .	1	0	0	1	8
Total . . . . .	10	4	3	17	39

\* Other than classical atopic dermatitis including: multiple lichen simplex chronicus, nummular eczema, exudative neurodermatitis, and so forth.

TABLE 5.—UNTOWARD REACTIONS WITH THIENYLENE

Symptom	No. reactions
Drowsiness . . . . .	10
Dizziness . . . . .	5
Vomiting and gastro-intestinal upset . . . . .	5
Headache . . . . .	3
Insomnia . . . . .	1
Nervousness . . . . .	1
Urinary difficulty . . . . .	1
Bitter taste in mouth . . . . .	1

6 of 12 felt benadryl and pyribenzamine, respectively, helped them. Here the patient's subjective valuation is paramount. The greater sedative effect of the benadryl probably accounts for its better showing. Patients with atopic dermatitis benefit generally from sedation and on direct questioning several of this group stated that they preferred benadryl to the others because of its greater quieting effect on them generally.

Thirty-nine patients received treatment with all 3 drugs at different times. Only 17 of this group expressed a definite preference for 1 preparation over the others. These preferences are listed in Table 4. This table is based entirely on the preferences of the patients. Although the patients who received treatment with all 3 drugs represent only a part of the whole group, it is somewhat surprising that the apparent superiority of benadryl in atopic dermatitis, as previously mentioned, is not evidenced by this group. Untoward reactions understandably figured largely in the patient's comparison of the drugs.

Untoward reactions to thenylene are listed in Table 5. A patient sometimes had more than 1 reaction. If such was the case each symptom has been noted so that in this table the number of times each reaction was experienced by the entire group is given rather than the number of patients in the group who noted reactions. Ten of the 126 patients, taking thenylene, complained of drowsiness as did 3 of the 47 taking benadryl, and 1 of the 44 taking pyribenzamine. For the most part drowsiness when it occurred with benadryl was more marked than

with either of the other drugs and relatively more patients who were taking benadryl experienced a slight sedative effect not classified as an untoward reaction. A patient who had benign prostatic hypertrophy had increased difficulty in voiding while he was taking thenylene, and he also experienced the same difficulty during treatment with both benadryl and pyribenzamine. The aggravation of the difficulty ceased with discontinuance of use of these drugs. In our group no serious toxic reactions were experienced although it was necessary to stop medication in several cases. Patients intolerant to one drug frequently could tolerate another. No cumulative effects were noted. Brom-sulfalein tests of liver function were conducted on 4 of the patients who had taken thenylene in daily doses of from 0.3 to 0.4 gm. for 9, 17, 36 and 43 days, respectively. There was no retention of dye in any of these cases.

**Summary and Conclusions.** A clinical evaluation of thenylene, a new drug with antihistamine properties, shows it to be of definite value in treatment of certain dermatologic conditions. Its most marked effect was in treatment of dermatoses, such as urticaria and angioneurotic edema which are characterized by cutaneous edema. With few exceptions oral doses of from 50 to 100 mg. 3 or 4 times a day led to lessening or disappearance of such edema. No cumulative effect was noted and untoward reactions were minimal. A clinical comparison of the results of treatment with thenylene, benadryl and pyribenzamine revealed a high degree of similarity

# ECCHYMOSIS OF THE ABDOMINAL WALL AS AN EARLY DIAGNOSTIC SIGN OF DISSECTING ANEURYSM OF THE AORTA

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ACUTE dissecting aneurysm of the aorta is seen rather infrequently. At the Massachusetts General Hospital 30 such cases were seen from 1897 to 1946,<sup>2</sup> and of these 30 cases, a correct antemortem diagnosis of dissecting aneurysm of the aorta had been established in 10.

It is not the purpose of this communication to reemphasize the clinical picture, nor to enumerate the symptoms and signs. These have been admirably done in literature and text. Rather it is concerned with the reporting of an observation heretofore not described or reported in the literature reviewed. It was of sufficient significance to establish a diagnosis of acute dissecting aneurysm of the aorta at a time when the clinical diagnosis seemed to be iliac embolism, and when the idea of operative interference was entertained. The literature contains reports of cases in which operative relief was attempted for supposed iliac thrombosis or embolism in which the phenomena associated with the latter were really a part of the picture of acute dissecting aneurysm of the aorta.<sup>2,3</sup>

**Clinical Abstract.** A white female, aged 52, without a history of previous illness or trauma, suddenly had severe non-radiating chest pain, followed in a few moments by lower abdominal pain, and shortly thereafter by pain in the left leg. She then noted numbness and tingling, and inability to move the leg. Examination 1 hour after the onset showed the pulse to be slow and regular. The blood pressure was 158 (systolic) and 68 (diastolic), measured in mm. of mercury. The heart sounds were distant. There was

pallor of the left leg, and it felt colder to the touch than did the right leg. There was absence of sensation to touch and pin. There was almost complete inability to move the leg. Femoral pulsation was absent on the left but present on the right side. The symptoms and findings, namely pallor, lowered surface temperature, loss of sensation and muscle power, and absence of pulsation in the arteries of the involved extremity, were typical of those found in embolism of the femoral or iliac arteries. Within one-half hour there appeared an area of purplish discoloration, about 10 cm. in diameter, in the skin of the left lower abdominal quadrant. The presence of this area of ecchymosis suggested the likelihood of the iliac obstruction being merely a part of a more extensive process; and that the ecchymosis represented bleeding from the left deep inferior epigastric artery. A diagnosis was thus made of a dissecting aneurysm of the aorta with involvement of the iliac artery and the deep inferior epigastric artery, the latter involvement producing the ecchymosis. Several hours later an area of ecchymosis appeared in the skin of the right lower abdominal quadrant. The patient had not voided for some 20 hours, and although the bladder was not distended, it was catheterized, 15 cc. of non-bloody urine being obtained. Since subclinical shock was not manifest for some hours after the onset, it was felt that the shock did not contribute entirely to the anuria, but that the renal arteries were involved in the dissecting process. Similarly, the stools contained fresh blood, suggesting involvement of the inferior mesenteric artery.

The patient became increasingly restless and cyanotic (the usual supportive therapy was given throughout, including transfusions of plasma and whole blood; oxygen, etc., and

\*This department is in part supported by the Michael Reese Research Foundation.

died 30 hours after the onset of the initial symptoms.

**AUTOPSY.** (Only the most important findings shall be mentioned.) The purplish discoloration which had been noted clinically was present in the skin over the lower abdominal quadrant. The subcutaneous tissue and the adjacent muscles also disclosed foci of hemorrhages. The peritoneal cavity contained approximately 1000 cc. of yellowish, slightly hemorrhagic, but otherwise clear liquid. Foci of hemorrhages were present just beneath the peritoneum of several loops of small intestine. The heart with the attached pericardium weighed 450 gm. The epicardium was covered with small fibrinous excrescences beneath which a number of minute hemorrhages were noted. These hemorrhages were particularly pronounced at the base of the heart and along the course of the coronary arteries. The ascending and descending aorta when inspected before opening, appeared purplish gray. The valvular apparatus was intact. The left ventricular wall measured about 13 mm. in thickness; the right, 3 mm. A number of sub-endocardial hemorrhages were noted in the right auricle and right ventricle. The myocardium was firm and reddish brown. Moderate to severe arteriosclerosis was found in both coronary arteries. Their lumens were patent. The aorta throughout its length, the proximal portions of the great vessels of the neck, the common and external iliac arteries and femoral arteries resembled a double barreled tube. The adventitia and media were separated by a moderate amount of partially liquid and clotted blood. Within the ascending aorta about 2 cm. above the anterior cusp of the aortic valve there was a Y-shaped ragged tear in the intima. This tear was present in an atheromatous ulcer which measured about 0.8 x 2 cm. in its greatest diameter. The surrounding intima was calcified and undermined by hemorrhagic material. The tear within the base of the ulcer communicated freely with the space between the media and adventitia of the aorta. The tear also communicated with various subepicardial spaces.

The dissection had extended into the femoral arteries and from there cranially along both inferior epigastric arteries. The dissection also involved both renal arteries and the mouth of the inferior mesenteric artery.

A number of hemorrhages were found throughout the mucosa of the transverse and descending colon, but were most pronounced in the sigmoid and rectum.

*Microscopic examination* of the aorta disclosed severe arteriosclerosis and a number of typical atheromatous ulcers. Nowhere was any evidence of syphilis or medial necrosis observed.

**SUMMARY.** At the autopsy of a 52 year old white female, marked arteriosclerosis and atheromatosis of the aorta was present with formation of atheromatous ulcers. One of these, located in the ascending aorta just above the aortic valve, had ruptured through to the media and caused a large dissecting aneurysm extending along the ascending aorta, arch, and descending aorta. From there the hemorrhage had extended along both inferior epigastric arteries and had produced a subcutaneous hemorrhage in the region of the lower abdominal quadrant.

**Discussion.** In this case of dissecting aneurysm of the aorta there was present an unusual clinical sign heretofore undescribed.<sup>1,4</sup> The immediate clinical picture was one of left iliac embolism, and surgical intervention was entertained. However, by virtue of the area of ecchymosis in the skin of the lower abdomen, it was felt that what first appeared to be a left iliac obstruction was merely a part of a more extensive process, and that the patient had a dissecting aneurysm, involving among other vessels the external iliacs, and extending on through the deep inferior epigastric arteries. Surgical intervention was thus obviously not undertaken. Autopsy revealed the anticipated involvement.

**Conclusions.** In a patient with findings indicative of acute embolic occlusion of the iliac artery, the presence of ecchymosis of the abdominal wall suggested the diagnosis of acute dissecting aneurysm of the aorta, the ecchymosis resulting from involvement of the deep inferior epigastric arteries. Pathologic studies confirmed this. To our knowledge, this observation has not been previously recorded.



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# THE CLINICAL USE OF A TRIPLE SULFONAMIDE MIXTURE

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ONE of the greatest advances in the use of sulfa drugs is unquestionably the recent introduction of multiple sulfonamide therapy. The investigations by Frisk, Hagerman and co-workers<sup>3,4,5</sup> and by Lehr<sup>7</sup> have shown that the solubility of a given sulfa drug in plasma and urine is practically not affected by the presence of other sulfonamides. Thus all the undesirable side reactions which are due to the rather low solubility of the various sulfa drugs can be greatly reduced if mixtures of several sulfonamides are given. While most of the clinical work so far has been restricted to combinations of 2 sulfa drugs,<sup>8,10,12</sup> it was only logical to extend this idea to triple sulfonamide mixtures. Such an extension is made possible by the fact that the 3 most commonly used drugs of this group, namely, sulfadiazine, sulfamerazine and sulfathiazole, are quite similar in their antibacterial activity and thus are interchangeable in the majority of conditions requiring this type of therapy. Frisk<sup>4</sup> has reported that such a triple sulfonamide mixture has been used in Sweden "in many hundreds of cases of acute pneumonia with good results and tolerance and without any known cases of renal calculi, also with increased doses in many cases of gonorrhea."

The main interest in multiple sulfonamide therapy has centered around the reduction of renal complications, particularly crystalluria. The latter has been reported to be present in from 26 to 28% when administering sulfadiazine or sulfamerazine alone.<sup>1</sup> It can be reduced to 6% when a combination of 2 drugs, sulfadiazine and sulfamerazine, is used,<sup>1</sup> and

it can be further reduced to below 3% when adequate amounts of systemic alkalinizers are added to a mixture of 2 sulfa drugs.<sup>12</sup>

In the present study, we have extended our investigation of multiple sulfonamide therapy to the use of a mixture consisting of sulfadiazine, sulfamerazine and sulfathiazole without any alkalizing salts. The preparation was composed of: sulfadiazine (microcrystalline), 3.5% (wt. vol.); sulfamerazine (microcrystalline), 3%; and sulfathiazole (microcrystalline), 3.5%; in an aromatized aqueous suspension base.\* The reason for supplying smaller proportions of sulfamerazine was due to the fact that this drug is excreted at a slower rate than the other 2 components and is, therefore, needed in smaller amounts.

The preparation was given to 28 unselected patients mostly surgical cases requiring sulfonamide therapy. The initial dose was from 20 to 40 cc., representing from 2 to 4 gm. of total sulfonamides followed by 10 cc. = 1 gm. of total sulfonamides every 4 hours. Blood samples were taken repeatedly during the treatment and urine specimens were collected from each voiding. The group consisted of 18 men and 10 women ranging in age from 16 to 74 years. Altogether 101 blood and 218 urine specimens were obtained and in all samples the concentration of free and total sulfonamides was determined. In addition all urine specimens were inspected microscopically for sulfa crystals (free and acetylated), and, when present, the crystals were identified by a qualitative chemical test.

The average blood concentration was

found to be 7.8 mg. of free and 8.5 mg. of total sulfonamides. These figures represent exactly the values which could be expected from the known average blood levels for each of the 3 sulfonamides if one considers their relative proportions in the medication. Thus it can be concluded that the absorption of each sulfonamide is not interfered with by the presence of the other components. This is in full accord with earlier observations by Oettinger and Cronheim<sup>12</sup> on dual sulfonamide mixtures.

while in most instances it was used as specific treatment. Penicillin in conjunction with the sulfonamide mixture was administered to approximately one-half of the patients. No serious side-effects were observed. In no case was it necessary to discontinue the drug. One patient complained of nausea throughout the course of therapy.

The urinalysis showed that over 80% of the specimens had an acid reaction. Unfortunately, it was impossible for tech-

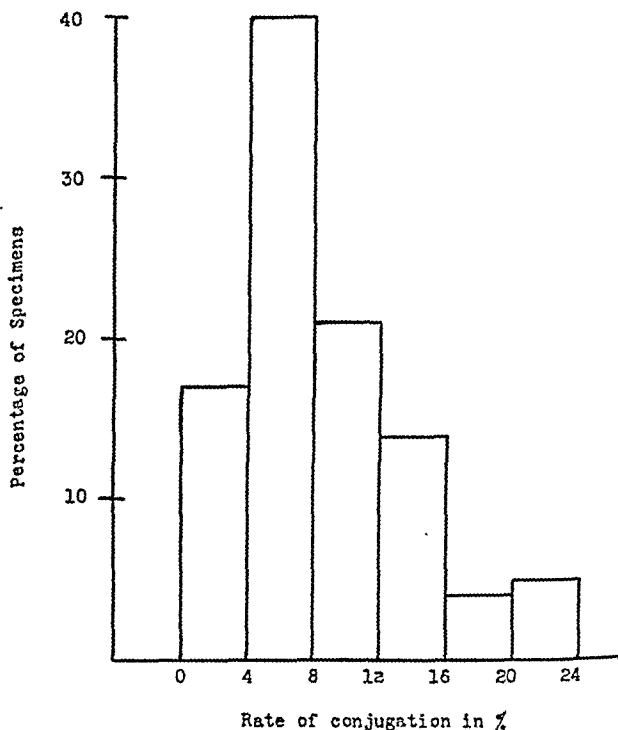


FIG. 1.—Acetylation of sulfonamides in Blood.

The figures also indicate that the acetylation of the sulfonamides in the blood is remarkably low, with an average of 8%. A more detailed distribution is shown in Figure 1. It can be seen that in more than half of all samples the amount of acetylated sulfonamides did not exceed 8%.

From a clinical standpoint, the attained blood levels were fully satisfactory, as evidenced by the fact that the patients responded to the sulfonamide therapy in the usual manner. In some instances, the preparation was given prophylactically

nical reasons to make accurate pH determinations or measure the total urine volume for complete excretion studies. However, the concentration of free and total sulfonamides could be determined in all specimens, thus giving accurate data for the degree of acetylation in urine. The figures indicate that an average of 83% of the excreted sulfonamide is in the free form. A more detailed breakdown on the data is presented in Figure 2. It shows that in about two-thirds of all urine specimens less than 20% of the ex-

creted sulfonamides were in the conjugated form. This indicates a lesser degree of acetylation than has been reported for single sulfonamides (Table 1).

The total number of urine specimens containing sulfa crystals was 6, corresponding to 3%. Three of these specimens were from 1 patient who during a previous illness had shown an unusual susceptibility to sulfa drugs. The other 3 samples were from 3 different patients. In each case the crystals were so few that they did not require interruption of the treatment, and were not found in subsequent urine samples.

**Discussion.** It is generally agreed that the main limitation in sulfonamide therapy has been the danger of kidney damage from the precipitation of the free or conjugated drug. While it is possible to reduce this danger by the simultaneous administration of alkali the amounts required to be effective are so great that they cannot be used indiscriminately for several reasons: they might lead to alkalosis, they present an additional load on the gastro-intestinal tract and the kidneys, and they are definitely contraindicated in patients with renal or cardiac insufficiency. In addition, large amounts

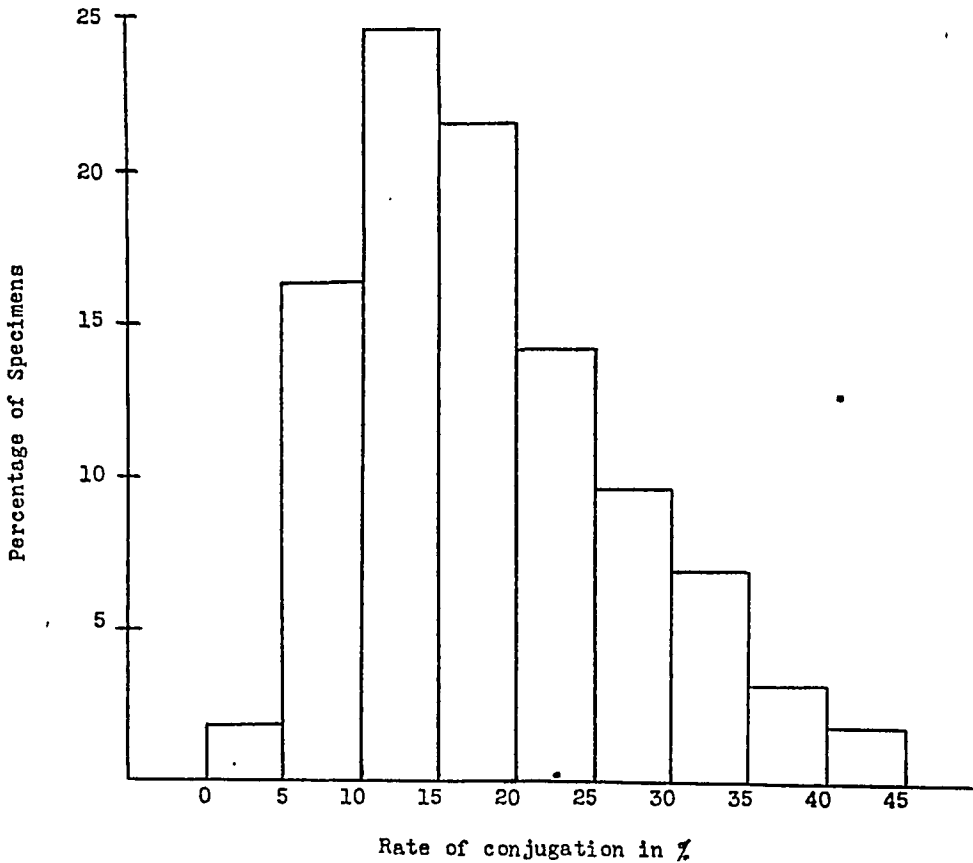


FIG. 2.—Acetylation of sulfonamides in Urine.

TABLE 1.—DEGREE OF ACETYLATION (%)

Drug	Blood	Urine	Reference
Sulfadiazine . . . . .	10	30	Wheeler <sup>16</sup>
	14	30	Reinhold <sup>14</sup>
	16	..	Flippin <sup>2</sup>
Sulfamerazine . . . . .	11-18	Over 40	Murphy <sup>11</sup>
Sulfathiazole . . . . .	12	14	Sadusk <sup>15</sup>
	24	26	Reinhold <sup>13</sup>
	28	..	Flippin <sup>2</sup>
Triple sulfonamide mixture . . .	8	17	Present investigation

of alkali depress considerably the blood concentration of sulfonamides<sup>6</sup> and thereby reduce the efficacy of the medication.

All these dangers are avoided when multiple sulfonamide therapy is used. Table 2 summarizes how the incidence of crystalluria is reduced. The figures clearly indicate the superiority of sulfonamide mixtures.

fonamides are conjugated responds, not to the total concentration of circulating sulfa drugs, but "processes" each sulfonamide as a separate chemical compound in accordance with its low individual concentration. Whatever the explanation might be, the fact that there is less acetylation should make multiple sulfonamide therapy more efficient since only

TABLE 2.—CRYSTALLURIA IN SULFONAMIDE THERAPY

Drug given during 24 hour period	Crystalluria (%)	Reference
4-6 gm. sulfadiazine . . . . .	28	Flippin <sup>1</sup>
4-6 gm. sulfamerazine . . . . .	26	Flippin <sup>1</sup>
4-6 gm. sulfadiazine + sulfamerazine . . . . .	6	Flippin <sup>1</sup>
4 gm. sulfadiazine + sulfathiazole + systemic alkalizers equivalent to 6.6 gm. of sodium bicarbonate . . . . .	3	Oettinger and Cronheim <sup>12</sup>
4 gm. sulfadiazine + sulfamerazine + sulfathiazole . . . . .	3	Present investigation

It should be pointed out that multiple sulfonamide mixtures not only reduce the incidence of crystalluria, but have other advantages which might prove to be equally important. Due to the greater tolerance of this type of preparation, it is possible to increase the total dose of sulfonamides so as to obtain higher blood levels. This is desirable not only in certain types of infections such as meningitis, where the drug has to cross the hematocephalic barrier and pass into the cerebrospinal fluid, but also in cases where the pathogenic organisms show an increased resistance to sulfonamides.

Another factor in favor of multiple sulfonamide therapy is the low rate of acetylation which has been found in this and earlier studies.<sup>8,10,12</sup> This applies to both blood and urine as can be seen from a comparison of the data presented in Table 2. The observations seem to indicate that the mechanism by which sul-

the free form of the sulfa drugs has a bacteriostatic action. This view is in full accord with the observations by Lehr and his co-workers who emphasized repeatedly the rapidity of the therapeutic response to mixed sulfonamides.

**Summary.** A mixture containing sulfadiazine, sulfamerazine and sulfathiazole in microcrystalline suspension has been studied with regard to absorption, excretion and crystalluria.

Adequate blood levels are maintained on the usual dosage schedule of from 2 to 4 gm. of total sulfonamides initially followed by 1 gm. every 4 hours.

The incidence of crystalluria is extremely low even though no alkali was administered in any form. In no case was it necessary to discontinue drug treatment.

The acetylation of the sulfonamides in both blood and urine seems to be noticeably reduced.

\* This preparation was supplied by the S. E. Massengill Company, Bristol, Tennessee.

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# CHOLESTEROL METABOLISM: BLOOD SERUM CHOLESTEROL AND ESTER LEVELS IN 200 CASES OF ACUTE CORONARY THROMBOSIS\*†

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The role of fat in the diet has recently aroused widespread interest as to its effect in producing atherosclerosis, arteriosclerosis, and by the same token, coronary artery disease. This report is the first in a series by the authors as a study in the role of the diet (particularly its fat component) the liver, blood plasma colloid disturbances, and the reticuloendothelial system in causing coronary artery disease and systemic arteriosclerosis.

Contradictory reports exist on the relationship of the blood cholesterol to atherosclerosis, coronary artery sclerosis and arteriosclerosis. Some authors report hypercholesteremia in these diseases and others report normal blood cholesterol levels. We believe that these discrepancies may be accounted for by differences in variable technical procedures, sex and age variations, uncontrolled dietary habits during the study and clinical diagnosis of the disease subject to marked variability in interpretations by the various authors.

It has been pointed out<sup>3</sup> that the blood serum cholesterol and the cholesterol ester are constant in normal

subjects and are accurate gauges of the blood lipid level. We therefore used the blood serum cholesterol and ester as an index of blood lipid concentration. If the fat in the diet should raise the blood lipid level the blood cholesterol and ester would correspondingly rise.

Certain recent reviews dealing with the etiology of coronary artery disease have ascribed considerable significance to disturbances in cholesterol metabolism<sup>5,10,13</sup>. This concept was originally proposed by Virchow<sup>15</sup> and by Aschoff<sup>2</sup> and was known as the Imbibition Theory<sup>15</sup>. This theory assumes that lipids from the plasma are absorbed directly through the endothelium into the intima and under certain conditions cholesterol and cholesterol esters are deposited there. Virchow believes that first the connective tissue ground substance of the arterial intima had to be weakened by mechanical strain. Aschoff emphasized the importance of increased blood concentrations of cholesterol and esters in atherosclerosis.

Klotz<sup>8</sup> and Leary<sup>9</sup> have advanced the concept of a disordered cholesterol

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metabolism also, but differ from the above theories in their belief that the lipids are brought to the vessel wall by cellular elements essentially within the vessel wall and are deposited there. Leary believes that there is some defense mechanism which removes excess cholesterol from the arteries. The cholesterol esters are transported from wandering "foam" cells to fixed fibroblasts in the arterial wall, thereby resulting in the cholesterol esters found in the vessel walls in arteriosclerosis.

Winternitz<sup>16</sup> has stressed that in atherosclerosis the intimal endothelium is seldom the site of disease; that the vasa vasorum or mural vascular channels in the arteries are the sites of hemorrhages and sclerosis, with later lipid deposition. This theory is not supported by most investigators at present<sup>6</sup>.

Hueper<sup>6</sup> has climaxed comprehensive search into the etiology and morphology of arteriosclerosis by concluding that the disease is found exclusively in colloidal disturbances of the lipoids and carbohydrates of the blood plasma. Hueper believes that there exist four fundamental types of anoxemic causative mechanisms in arteriosclerosis: (1) changes causing either hypertonus or hypotonus of the vascular walls; (2) changes in the hydrostatic intravascular pressure, such changes causing hydrostatic hypertension or hypotension; (3) changes in the colloidal plasma composition and resulting equilibrium; these changes involving plasma lipids, proteins and carbohydrates and being both quantitative and qualitative in nature. Thus the exchange of gases and nutritive substances would be disturbed; and (4) changes in the oxygen-carrying power and in the oxygen-carbon dioxide balance of the blood and its tissues.

Anitschkow<sup>1</sup> demonstrated that the atheromatous plaque or typical arteriosclerotic lesion is a deposition of lipids

which takes place primarily in the tissue spaces of the arterial intima between the superimposed endothelium and the underlying barrier of the fenestrated internal elastic membrane of the artery.

Various data have been presented in both support and refutation of the above concepts. As stated previously, contradictory results have resulted from variable factors which the present authors have attempted to avoid.

Recent studies appear to lay greater significance on the role of the blood lipids, these including cholesterol and cholesterol esters. It is planned to explore further the role of fat in the diet as the cause of coronary artery disease and arteriosclerosis.

It is well-known that the clinical, electrocardiographic, laboratory and X-ray diagnosis of atherosclerosis and arteriosclerosis are subject to variable interpretation. Only post-mortem or conclusive evidence of acute coronary occlusion is acceptable as a final proof that coronary artery arteriosclerosis is present.

Arteriosclerosis is now the leading cause of morbidity and mortality. Arteriosclerosis, particularly of the coronary arteries is the leading cause of death in the United States of America with a total of 355,000 victims in the 1940 statistics. Joslin<sup>7</sup> estimates the mortality from arteriosclerosis in Massachusetts to be 37% of the total deaths.

The following studies of pre-mortem and post-mortem coronary artery occlusion and its possible relationship to disturbed cholesterol metabolism are therefore presented. This may be of particular importance because of the power of the liver actively to remove cholesterol and fat from the blood, of storing it within its substance<sup>4,12</sup>, and of synthesizing and destroying cholesterol.

In view of the conflicting views re-



garding the presence of hypercholesterolemia in coronary artery disease, the authors examined a series of 200 cases of acute coronary thrombosis admitted to the wards of the Los Angeles County General Hospital. These cases were all unselected and taken in the order of their admission to the hospital.

It has been recognised by recent authors that many of the inconsistencies in blood cholesterol determinations have been due to the unreliability of certain methods which have been widely employed. This subject has been adequately reviewed elsewhere<sup>12,14</sup>. Accordingly, a modification of the Sperry-Schoenheimer method has been employed for both cholesterol and cholesterol ester determination. A recent modification has been published by Sperry and Brand<sup>14</sup> and a further modification has been made by one of the authors (A. L. C.) in a method to be published. These modifications have been checked against the original Sperry-Schoenheimer method and also against other procedures in wide use. These results again emphasize the necessity for adherence to the basic

of the original Sperry-Schoenheimer procedure without at the same time sacrificing any of its accuracy.

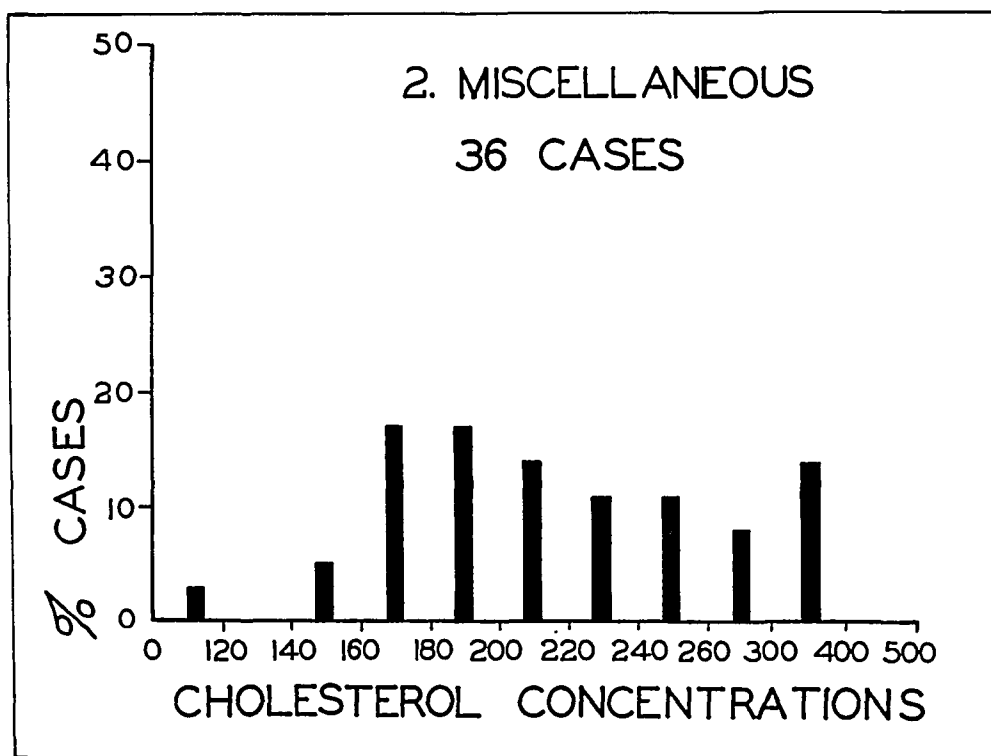
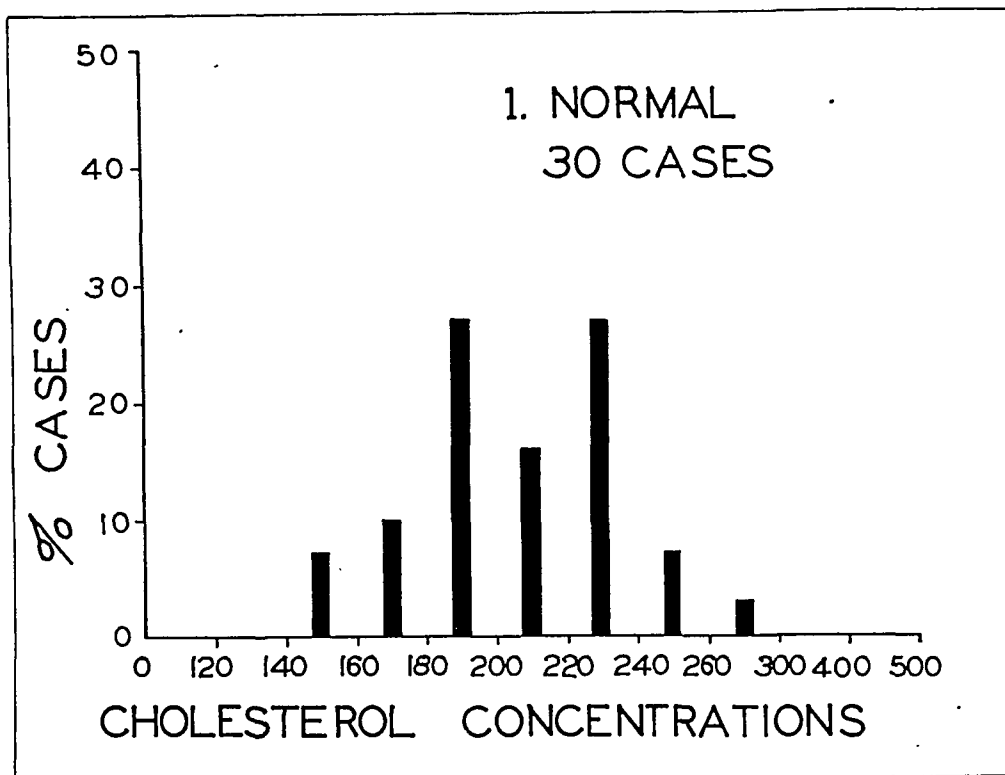
**Clinical Material.** Three series of cases are presented here. First, a series of 30 normal controls for comparison with other published series. The second is a series of 36 cases on patients having a wide variety of diseases for comparative purposes. Third, a series of 200 cases of acute coronary occlusion, most of whom survived their initial attack, are analyzed. Included are some cases which were examined post-mortem. The following table shows the distribution of cholesterol values obtained in each series. Table 1 presents a summary of the cholesterol values obtained in the three series of cases. In addition, the average age for each group of cholesterol values is shown for the coronary occlusion series. The cases were 90% Caucasian in race, the remainder being either Negro or other races.

Of the cases of coronary occlusion, 75% were males, 25% females and the ages ranged from 28 to 84. Blood cholesterol levels were taken within 48

Serum Cholesterol Conc.-Mg/100 cc	Normal Cases	% of Total	Miscellaneous Cases	% of Total	Coronary Cases	Occlusion % of Total	Average Age
80-139	0	0	1	3	2	1	70
140-159	2	7	2	6	2	1	81
160-179	3	10	6	17	17	8.5	70
180-199	8	27	7	20	18	9	70
200-219	5	17	5	14	31	15.5	65
220-239	8	27	4	11	22	11	61
240-259	2	7	4	11	12	6	61
260-299	1	3	3	8	31	15.5	63
300-399	1	3	5	14	55	27.5	53
400-	..	..	..	..	5	2.5	50
TOTAL	30	100	36	100	200	100	61

principles of the Sperry-Schoenheimer procedure and show that widely varying results may be obtained by other procedures which do not satisfactorily control the Lieberman-Burchard color reaction. The modification used in the series of cases to be presented appreciably shortens the time of determination and reduces the complexities

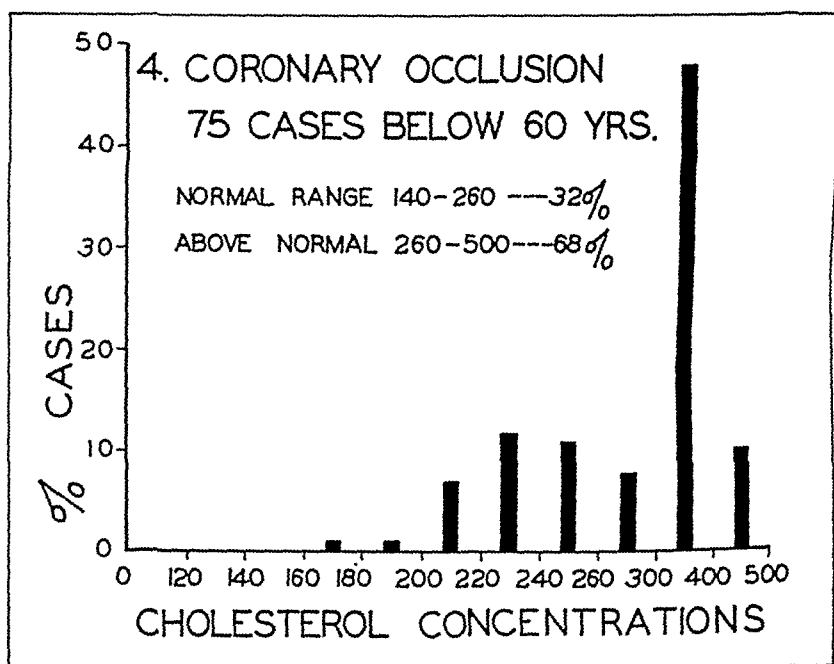
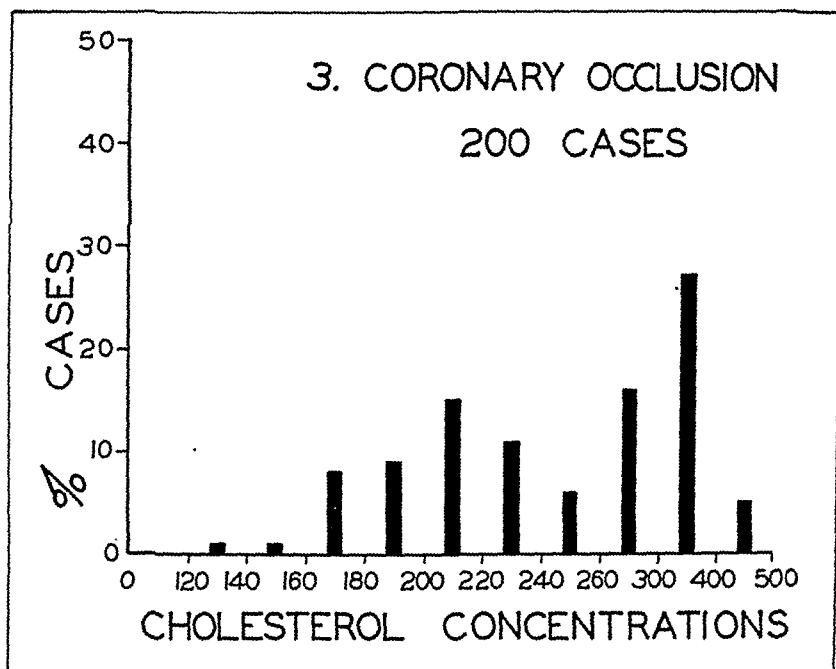
hours of admission, following the proven acute coronary occlusion and followed in a large percentage of cases with several subsequent determinations at 2 to 6 week intervals. Each case was definitely diagnosed as one of acute coronary occlusion both by the electrocardiographic report and the clinical examination. Both total and



free cholesterol determinations were made on all cases.

**Results.** The distribution of cholesterol values is most readily seen in the following series of figures. Figure 1 shows the distribution of cholesterol

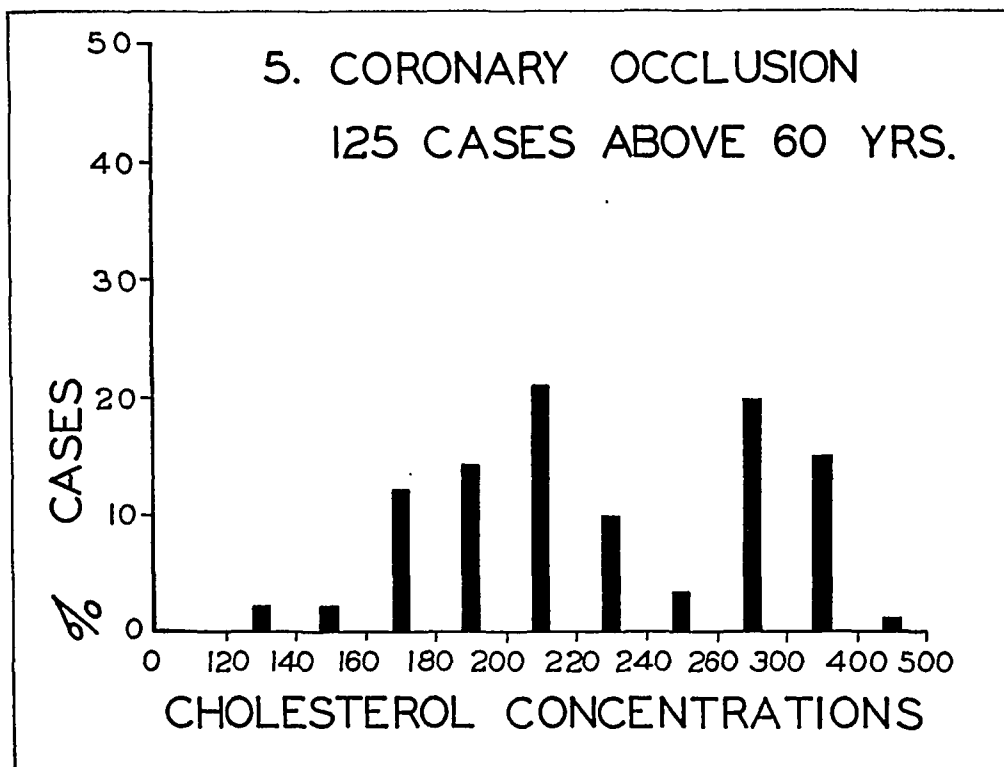
values for the normal series and it is seen that all but one case, or approximately 97%, are within the range of 150-260 milligrams per 100 cc. This distribution is similar to that published by Peters and Man<sup>11</sup>. The percentage



of free cholesterol ranged from 20 to 35% (average 28%).

Figure 2 shows the distribution of cholesterol values obtained in the miscellaneous series of 36 cases. It may be seen that the distribution here cor-

responds closely with that of the normal series except for 5 cases with values above the normal range. These cases, incidentally, were all in conditions recognised as being associated with disturbance of cholesterol meta-



bolism, such as biliary cirrhosis, myxedema and diabetes.

The distribution of cholesterol values for the series of coronary occlusion, shown in Figure 3, is seen to be distinctly abnormal. The distribution is such as to indicate a division of the cases into two distinct categories, those in which the cholesterol values are distributed in a normal manner, and an additional class in which the cholesterol concentration is distinctly elevated. It may be concluded from these results that high cholesterol values may be an etiological factor in many cases of coronary occlusion, but other cases occur in which it would appear that cholesterol metabolism may not be involved.

These results are shown even more contrastingly in Figures 4 and 5 in which the cases have been divided according to age. Figure 4 shows a series of 75 cases below the age of 60 and in these it is seen that nearly 70% of the cases have elevated blood cholesterol. In the cases above the age of 60 (Figure 5) this tendency is not

nearly so prominent, about 48% being elevated and about 52% in the normal range.

The distribution of cholesterol between the free and the ester form was not markedly changed in this series of cases. The average percent of free cholesterol was 30 compared to 28% in the normal. It does not appear that the mechanism for esterification of cholesterol is involved in this disease entity.

A study of the series with respect to sex distribution does not indicate any marked trend with the exception of the fact that these cases of coronary occlusion were 75% males. The interrelationship of age and cholesterol concentration is also shown in Table 1, in which the average age for each level of cholesterol concentration is given. It is there readily seen that coronary occlusion appears earlier in cases having high cholesterol values.

**Summary and Conclusions.** 1. A consecutive unselected series of 200 patients with acute coronary occlusion

was studied for blood cholesterol and cholesterol ester levels within 48 hours after hospital admission.

2. In 68% of 75 patients under 60 years of age with proven acute coronary occlusion hypercholesterolemia was present.

3. In 52% of 125 patients over 60

years of age with proven acute coronary occlusion a normal cholesterol level was found.

4. Coronary thrombosis in patients under the age of 60 is frequently associated with hypercholesterolemia and disturbances of cholesterol metabolism.

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# PHEOCHROMOCYTOMA OF THE ADRENAL MEDULLA

A Clinicopathological Study of Five Cases

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PHEOCHROMOCYTOMA is a relatively unusual lesion. The present series of 5 cases is one of the largest groups reported from a single institution at any one time, and includes the ninth case on record of bilateral malignant adrenal pheochromocytoma.

Our purpose in this paper is to present several clinical types of pheochromocytoma and to correlate clinical and pathologic findings where this is possible. The different types referred to are: (1) malignant adrenal pheochromocytoma with metastases; (2) benign adrenal pheochromocytoma with hypertension (paroxysmal or sustained); (3) benign adrenal pheochromocytoma found incidentally at autopsy with no clinical signs or symptoms.

General considerations of location of chromaffin tissue, from which these tumors arise and the embryology of this tissue having been adequately discussed<sup>5,10,12</sup> elsewhere will not be considered further here.

In the present series of 5 cases there are 3 males and 2 females. The age incidence varies from 30 to 61 years. Three of the cases occurred between 51 and 61 years of age. The malignant tumor occurred in the 51 year old female. The age and sex incidence of this group is similar to that of previously reported cases.<sup>5</sup>

Association of hypertension with pheochromocytoma is well known.<sup>2,5,9,16,18,20</sup> When hypertension is present the clinical correlation on the basis of present theories is good, *i. e.*, the elaboration of a pressor substance by the tumor cells,<sup>1</sup> causing hypertension which is paroxysmal or sustained. However, there are cases in the

literature<sup>12</sup> as well as in the present series, in which this symptom is not present. The absence of hypertension in these cases makes it more difficult to accept the above mechanism as the only one involved.

The details in the case reports below are included only if thought to be connected with the subject under consideration.

*Case Reports.* CASE 1. R. W., a 51 year old white female, was apparently in good health until 2 months prior to admission, when she began to have headaches, chiefly occipital, mild in the morning and more severe later. The patient was dizzy and weak and fell repeatedly during the month before admission. Her memory was poor. She walked leaning to the right and fell frequently for 10 days before admission. During the last week the patient also complained of a stiff neck with increasing drowsiness, and slept almost constantly. There were generalized convulsions on the morning of admission.

*Physical Examination.* The blood pressure was 160/100. On admission, the patient was drowsy, comatose and did not respond to questions. The pupils were large, irregular and equal and did not respond to light. There was weakness of the left side of the face and rigidity of the neck. The left arm was completely flaccid. The deep reflexes were everywhere diminished, but weaker on the left. The abdominal reflexes were absent and there was no appreciation of pin-prick anywhere. There was bilateral papilledema. The clinical diagnosis was: "rapidly developing intracranial neoplasm, probably in the right frontal area."

*Course in the Hospital.* On lumbar puncture done on the 2nd hospital day, initial

pressure was 330 mm. (water) and final pressure 114 mm. Ten cc. of bloody spinal fluid was removed. There were 52 cells per c.mm., of which 10 were polymorphonuclears and 42 lymphocytes. A right subtemporal decompression was done on the 4th hospital day. On the following day, the patient's condition was poor and her blood pressure was 144/94. Three days later she became stuporous and remained so until she expired. Her blood pressure fell steadily until it reached 102/76 on the last day.

peduncles, cerebellum, pons, medulla and cerebrum. Some nodules were confluent, others small and containing a central area of softening. A preparation from the cerebral cortex showed large islands and cords of various sized and shaped cells, with nuclei that varied greatly in staining reaction. The latter were of a bizarre appearance, being ovoid or stellar and either peripherally or centrally placed. The nuclei contained a loosely arranged chromatin network and well-formed nucleoli. These islands of tumor

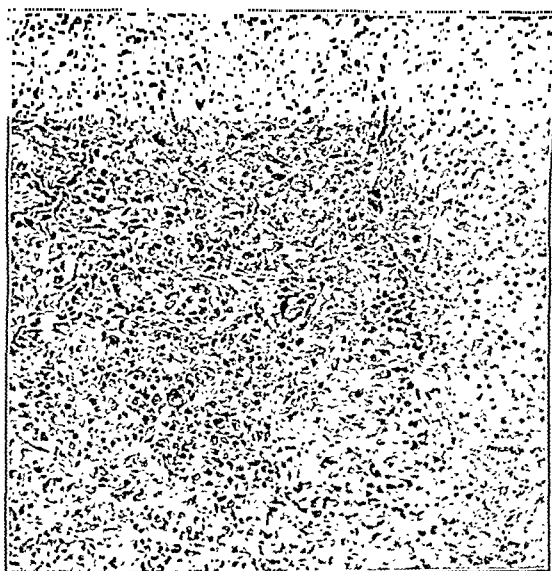


FIG. 1.—Case 1. Photomicrograph of tumor in adrenal gland. Note adrenal tissue on right side. (H. and E.  $\times 100$ .)

**Laboratory Data.** Spinal fluid protein was 154 mg. %; the globulin was 1+. The blood sugar, blood urea and urine examinations were not remarkable. The hemoglobin and red cell count normal; white blood cells, 18,900 (69% polymorphonuclear leukocytes, 26% lymphocytes and 5% monocytes).

**Morbid Anatomy.** (N39-210.) The heart (330 gm.) showed left ventricular hypertrophy and myofibrosis. The lungs showed local pneumonia, edema and an infarct in the right lung base. In 1 of the main branches of the pulmonary artery was a blood clot firmly attached to the vessel wall.

**Brain** (1385 gm.). The cut surfaces of the cortex and medulla contained homogeneous yellow and gray, well-circumscribed nodules, some of which were mottled with red. These were present in the cerebral

tissue were separated by distended endothelial lined spaces and homogeneous pink staining granular material. The perivascular spaces in these regions were increased in size and number and contained accumulations of round cells. Preparations from the pons, cerebellum and medulla showed a similar picture.

The right adrenal measured 5 by 4 by 0.9 cm. and weighed 7 gm. The cortex and medulla were well demarcated. The left adrenal measured 7 by 3 by 1.2 cm. and was grossly similar to the right. Microscopically, the adrenal glands were not remarkable except for the small nodules present in the medullæ of both glands. These showed identical histologic pictures. The cells were large, irregular, polyhedral, of a bizarre appearance, varying in size, and staining reac-

tion of the nuclei. The nuclei were vesicular, round, ovoid, triangular or stellate, and contained well-formed nucleoli. The cytoplasm was abundant and finely granular. Scattered in the vicinity of the tumor cells were collections of round cells and a few isolated plasma cells. The medullary layer was scanty and fairly well demarcated from the cortex which was compressed in the area around the nodule. The blood-vessels were distended and thick-walled and the capillaries were markedly engorged. Preparations stained with chromic salts showed a clear affinity of the stain for the tumor cells.

myofibrosis cordis; congestion of viscera; arteriosclerosis, generalized.

The above case is the ninth record of malignant bilateral adrenal pheochromocytoma and it is the only reported case with metastases to the brain. Practically all previously reported cases of malignant lesions had a normal blood pressure.<sup>5,11,15,20</sup> In this case (see Table 1) the blood pressure readings were somewhat elevated during the patient's hospital stay. However, the high readings may be explained by increased intracranial pressure (330



FIG. 2.—Case 1. Photomicrograph of metastasis in the brain. (H. and E.  $\times 100$ .)

TABLE 1.—BLOOD PRESSURE DURING HOSPITAL STAY (CASE 1)

Admission	2nd day	3rd day	4 h day (decompression done)	5th day	6th day	7th day	8th day	9th day	10th day
160/100	140/90	150/96	160/110	182/104	152/70	140/80	130/76	116/80	102/76
	146/94	178/90			130/68	134/80	140/80		

*Anatomic Diagnosis.* Pheochromocytoma in adrenal glands with metastases in brain; wound of recent subtemporal decompression (right); pneumonia, focal, bilateral; edema of lungs; petechiosis of pleura (right); thrombosis in branch of pulmonary artery (right); infarct in lung (right); dilatation of heart;

mm. of water on spinal tap) with accompanying hypertension and slow pulse. From the table below it will be seen that the blood pressure began to drop shortly after decompression was performed and continued to drop until the death of the



patient. Thus, this case is very similar to the other reported cases of malignant pheochromocytoma except for the location of metastases. It may be well to point out that, as in the previously reported cases,<sup>18</sup> the tumor was present in both adrenal glands.

The general absence of hypertension in the malignant pheochromocytoma has not been explained. It is probable that many of the malignant cells do not have the property of secreting the pressor substance as do the cells of the benign tumor. It would be interesting to try to demonstrate this pressor substance in the blood of a patient with malignant pheochromocytoma as was done by Beer *et al.*,<sup>1</sup> in a case with a benign lesion. This unfortunately was not done.

Histologically the structure of the malignant tumor was similar to that of the benign lesion, so that cellular structure alone cannot be used as a reliable criterion of malignancy in this type of tumor. We are in agreement with other authors that the only indication of malignancy is the presence of metastases.

The second case in our series is the forty-ninth reported case<sup>4,8</sup> of benign pheochromocytoma proven by cessation of symptoms after operation. This case is being reported in greater detail in another publication. It demonstrates a fairly typical clinical history.

CASE 2. B. S., 34 year old white female, about 11 months before admission, had occasional severe generalized headaches, vomiting and irritability. She was comparatively well after that until just before the termination of her pregnancy (1 month before admission), when she again developed headaches and some dizziness. During this last pregnancy, blood pressure, urine and blood chemistries were within normal limits. The day after delivery (2 weeks before admission) the patient developed severe headache, retching, vomiting and dizzy spells brought on by alteration in posture. These symptoms persisted. The neurologic examination, 1 week before admission, was negative. The patient became more drowsy, and 3 days

later a neurologist noted restlessness followed by left hemiparesis.

*Physical Examination.* The patient was semicomatose and somewhat disoriented. She ignored the existence of the left side of her body and exhibited the right hand and leg when asked to show her left. Her eyes deviated to the right and were unable to move to the left of the midline. There was slight blurring of the optic disk margins and left hemianopsia. Sensation on the left side of the body was diminished. The Babinskis were positive bilaterally and the deep reflexes were hyperactive on the left side. The urine examinations, blood counts, blood chemistries and serology were not unusual. Lumbar puncture showed an initial pressure of 300 mm. of water, and a final pressure of 170 mm. of water. The fluid was clear and no cells were seen. The spinal fluid protein was 50 mg. %, with a trace of globulin.

*Course.* Within the next few days the patient became better oriented; her memory improved and she demonstrated her left hand by picking it up with her right. The ventriculogram was negative. The patient continued to have bouts of nausea, but her mental status improved and the left hemiparesis was less marked. Eye examination revealed well-outlined optic disks, with some hemorrhage into the left disk. Visual fields revealed left homonymous hemianopsia. The patient left the hospital with residual hemiparesis, spacial disorientation and occasional nausea. Blood pressures, taken twice daily during her hospital stay, varied from 84/60 to 166/124. Most values were around 110/65.

Second admission (1 year later): A month after her last admission the patient was having attacks of nausea, with blood pressure up to 260/180. The urine examination at this time revealed 2+ albumin and casts. Since then, her blood pressure varied greatly from 90/40 to 280/190, and the transition from low to high blood pressure was observed within 5 minutes. Two months before the second admission, the patient's vomiting recurred and was accompanied by severe frontal headaches. The blood pressure was 190/150 during 1 attack. These attacks continued until admission.

*Physical Examination.* The blood pressure was 178/110 and the pulse 108 per minute. There was increased muscle tone on the left side of the body with "claw hand"

on the left. The motor power of the upper and lower extremities on the left was diminished. There were hyperactive tendon and superficial reflexes on the left side. The laboratory work and Roentgen rays of the chest were negative. The glucose tolerance test showed a normal curve.

pressure during the last episode was 190/140. A spinal tap showed a normal pressure. Cell count, chemistry and serology were normal. The patient remained unresponsive until the next day. A neurologic consultant saw the patient several days later and she had only the residual left hemiparesis. It was

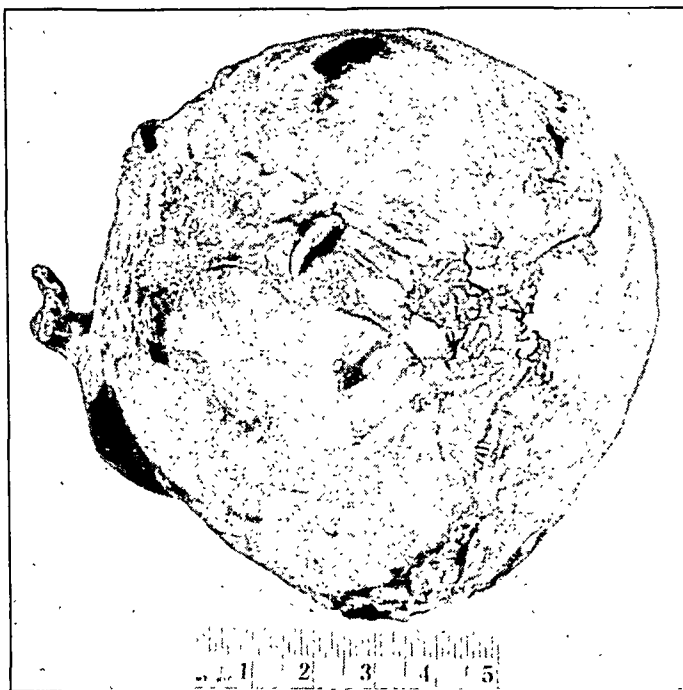


FIG. 3.—Case 2. Photograph of gross tumor.

*Course.* The patient had a left-sided clonic convulsion, lasting 45 seconds, followed by profuse perspiration. The blood pressure at this time varied from 100/80 to 240/180 within 3 minutes, with a pulse of 110 to 120. Intravenous pyelogram and retrograde pyelogram showed the right pelvis and calyces somewhat deformed. The kidney outline was normal. Perirenal insufflation was done, but the patient became markedly cyanotic and nauseated, with a very rapid pulse after 230 cc. of air was injected. The examination was discontinued and the patient recovered quickly. About 2 hours later the patient had a clonic seizure lasting about 40 seconds, involving the right arm and leg. The eyes were deviated to the left, the jaws were clenched and the patient was "foaming at the mouth." Five minutes after the seizure, she was lying relaxed with her eyes closed. The right Babinski was positive and the blood pressure was 106/84 at that time. There were similar episodes  $\frac{1}{2}$ ,  $\frac{3}{4}$  and  $2\frac{1}{2}$  hours later. The blood

thought that the episodes mentioned above could be explained on the basis of vascular spasm, possibly reflexly stimulated by perirenal air insufflation. The clinical impression was pheochromocytoma, and at operation a globular cystic tumor was removed from the right adrenal area. Her postoperative course was uneventful and she was discharged  $2\frac{1}{2}$  weeks later.

The patient returned to the hospital subsequently over a period of 3 years because of "claw hand" and contracture of the foot both on the left side. The blood pressure, 1 year after operation was usually about 120/90; 3 years after operation it was 110/70. There were no attacks of any kind since operation. The patient's blood pressure during her 2nd hospital day varied from 94/78 to 220/150 except for 2 days postoperatively, when the blood pressure hovered around 78/50.

*Surgical Pathology.* (S.P. 43-889.) The tumor removed at operation was a cystic mass measuring 1.05 by 10 by 4.5 cm. and

weighing 310 gm. The external surface in some areas was smooth and glistening, and in other areas it was covered by adipose and fibrous tissue tags. At one end of the specimen was attenuated adrenal glandular tissue. On section, the cyst contained clotted blood and friable soft, pale brown tissue. The inner surface of the cyst was yellow and smooth and measured up to 2 cm. in thickness. Between the outer and inner surfaces was soft pale pink and brown tissue. In the region of the adrenal remnant, section revealed a narrow rim of ochre-colored cor-

tex, with a pale brown medullary zone, which was poorly demarcated from the underlying tumor tissue. In 1 preparation, bordered by a capsule of hyalinized fibrous connective tissue, there was a fairly broad zone of adrenal cortex, in which the different cortical zones were well demarcated. In many cells, the cytoplasm was vacuolated, while in others it was clear and acidophilic. The medulla was replaced by tumor tissue, which showed a variegated picture. In some areas the cells were in an alveolar arrangement and were, for the most part, small,

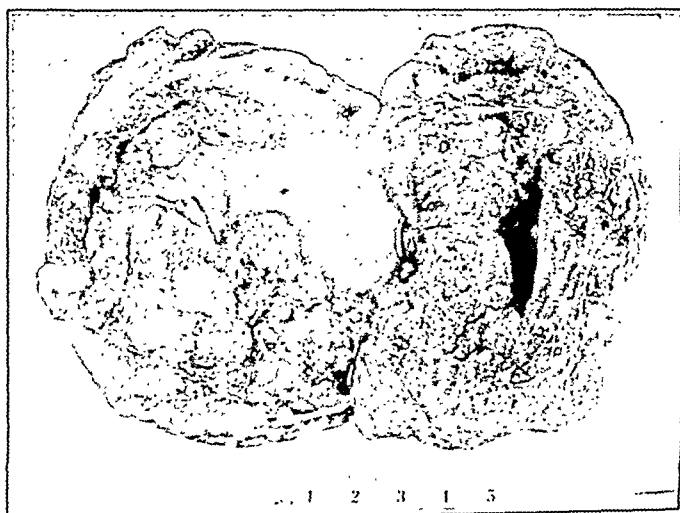


FIG. 4.—Case 2. Photograph of cut sections of tumor.

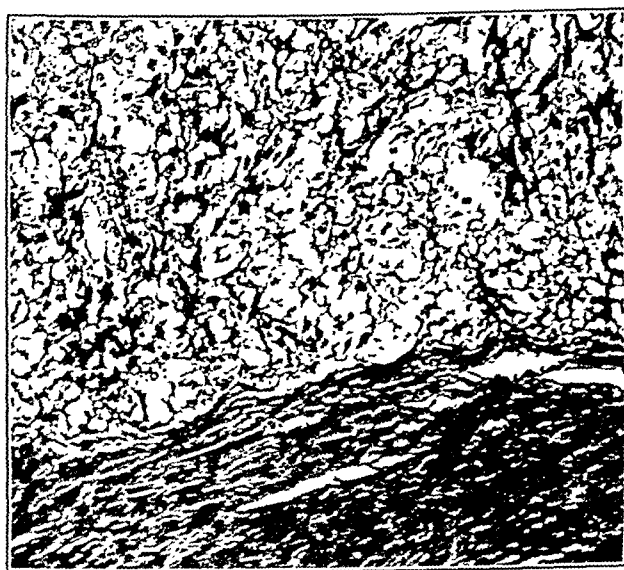


FIG. 5.—Case 2. Photomicrograph of tumor. Note the dense capsule. (B. and E.  $\times 100$ .)

with deeply staining round nuclei, acidophilic cytoplasm and distinct cell borders. In other areas the cells varied more widely in size and shape; most of them were irregularly polygonal with granular or clear cytoplasm, distinct cell outlines and round or oval vesicular nuclei. Some cells contained more than 1 nucleus. The stroma was scanty and vascular. With the chromaffin stain the nuclei were blue and the cytoplasm stained a yellow green. Separating the lobules in places were broad bands of connective tissue. Other preparations showed a similar picture. This was diagnosed as a pheochromocytoma of the right adrenal gland.

The neurologic signs and symptoms which were present at the first admission were probably due to a cerebral hemorrhage resulting from the hypertension. The ensuing hemiparesis improved, but contractions of the left hand and foot remained. However, over a period of 3 years after removal of the tumor, the patient's blood pressure has remained within normal limits. There has been no evidence of new lesions in the fundi, kidneys or brain, which one might have expected if the hypertension had remained. This patient is now comparatively well despite a major cerebral vascular accident over 3 years ago.

The convulsions which occurred during the patient's 2nd hospital stay were either the result of cerebral vascular spasm or were rapidly successive paroxysms of hypertension, more likely the latter.

The diagnosis in this case was much easier clinically than in Case 3, because of the more or less typical paroxysms which were present here.

In view of Smithwick's finding that 0.5% of 1000 hypertensive patients had pheochromocytomata (cited by Goldenberg *et al.*<sup>7</sup>), the diagnosis of this lesion has increased importance. Furthermore, it is likely that the incidence of this lesion is even higher, since Smithwick probably did not explore the remainder of the chromaffin system in these patients and these tumors may occur anywhere in this system.

CASE 3. A. D., a 55 year old white male, was admitted with a history of vomiting,

disorientation and collapse of 30 hours duration. About 30 hours before admission, the patient was found lying on the floor in a pool of vomitus. He was confused, restless and disorientated. He was admitted to another hospital where a spinal tap was done. The specimen, later sent to this hospital, was grossly bloody. The morning of admission the patient was still vomiting occasionally and complaining of slight headache and stiff neck. He became less confused and less restless shortly after admission. The patient had a hypertension of over "200" for several years. There were no previous similar episodes. He had moderate exertional dyspnea for 2 years and glaucoma for many years.

*Physical Examination.* The patient was a well-developed and well-nourished, confused, restless, white 55 year old male with slurred speech. His neck was stiff and the pupils were pin-point. There was increased intraocular tension bilaterally. The left cardiac border was about 1 cm. to the left of the midclavicular line. The clinical impression was subarachnoid hemorrhage; hypertensive cardiovascular disease with mild decompensation and chronic glaucoma.

*Course.* The patient's blood pressure and temperature rose steadily during the 5 days of his hospital stay. On the day following admission he was stuporous and spinal fluid was bloody with increased pressure. Two days later there were general hyperreflexia and marked rigidity of the neck. He complained constantly of headache and dizziness. The initial spinal fluid pressure at that time was 320 mm. of water; the final pressure was 130 mm. of water. The fluid was bloody. The patient expired the next day.

*Laboratory Data.* The only relevant data includes a white blood count of 19,000 (80% polymorphonuclears, 14% lymphocytes, 5% monocytes and 1% eosinophils).

*Morbid Anatomy.* (N38-115.) Pupils were unequal. There was a generalized arteriosclerosis. The heart (570 gm.) showed hypertrophy and dilatation with myofibrosis. The lungs showed hemorrhages in the pleura, emphysema and pneumoliths. In the cardia of the stomach there was a shallow ulcer 3 cm. in diameter. The brain (1500 gm.) gave no gross evidence of hemorrhage. In a preparation from the right temporal lobe the meninges were infiltrated with extrava-

sated blood. Numerous large mononuclear cells were seen loaded with brown pigment. A small amount of blood was present in the fourth ventricle. In a preparation including the inferior longitudinal fissure, the latter was filled with blood and brown pigment. Large numbers of polymorphonuclears were seen in places, and blood was seen in the adjacent cortical tissue. The aqueduct of Sylvius contained small clumps of bacteria, old blood and large mononuclear cells laden with brown pigment.

The right *adrenal* gland measured 6 by 3 by 1 cm. and weighed 8 gm. In the cut surfaces the cortex and medulla were well

arranged in irregular fashion. The cell boundaries were indistinct. The cytoplasm was abundant and homogeneously pink and the nuclei were large and round or oval. Most of them were vesicular and contained large dark nucleoli. Numerous cells attained a giant size and contained 1 or more bizarre shaped nuclei which varied considerably in chromatin content. Some of the nuclei contained large pale vacuoles. Mitotic figures were fairly numerous. Many capillaries and delicate connective tissue strands separated the cell groups. The tumor tissue blended into the rim of medullary tissue which partially surrounded it. The



FIG. 6.—Case 3. Photomicrograph of tumor in adrenal gland. Note adrenal gland in lower right corner. (H. and E.  $\times 100$ .)

demarcated and the latter was abundant. In the middle of the superior portion there was a large soft nodule 1 cm. in diameter, the cut surfaces of which were composed of a dark red center with a pink narrow rim. The left *adrenal* gland (6.5 by 2.5 by 1.5 cm.; weight, 9 gm.) showed cortex and medulla well demarcated. Microscopically, the left adrenal gland was not unusual. In a preparation from the red nodule seen grossly in the right gland, the medullary tissue was abundant. Within the medulla, in a large rounded area, were sheets and groups of irregular cells which resembled epithelium

cortical cell layers were compressed in many places.

*Anatomic Diagnosis.* Arteriosclerosis, generalized; hemorrhages, cerebral and pontine; hemorrhages in pleura with hemothorax (left); old and recent pericardial hemorrhages with hemopericardium; hypertrophy and dilatation of heart; myofibrosis cordis; passive congestion of viscera; pheochromocytoma of right suprarenal gland.

The pheochromocytoma in this case was unsuspected until autopsy. However, this patient had a long history of sustained

hypertension with a systolic blood pressure of over "200." It is true that there is no history of paroxysmal hypertension or any symptomatic paroxysms which may be associated with hypertension in these cases. Nevertheless, it is probable that the hypertension and the associated changes in this case was due to the pheochromocytoma. Similar cases were reported by Green<sup>9</sup> and Thorn.<sup>19</sup>

The life of the patient in this case might have been saved had the diagnosis been made before his cerebral hemorrhage. The possibility of pheochromocytoma must be kept in mind in studying any case with hypertension, whether it be labile or continuous. There are 2 tests which have been used as diagnostic procedures which seem relatively simple and which do not carry the danger of perirenal air insufflation. These are the histamine test of Roth and Kvale<sup>17</sup> and the more recent use of benzodioxane by Goldenberg *et al.*<sup>7</sup> These tests should prove useful when the diagnosis of pheochromocytoma is suspected.

**CASE 4.** E. M., a 40 year old white male, was admitted complaining of pain in the throat, blood-streaked vomitus and abdominal pain. He swallowed 23 gm. of bichloride of mercury about  $\frac{1}{2}$  hour before admission. There was no past history of hypertension or any other illness.

**Physical Examination.** The patient was acutely ill, with cyanotic face, lips and ears. The abdomen was moderately distended and diffuse tenderness was present. The blood pressure was not recorded on admission.

**Course.** On the 3rd hospital day his condition was poor. He was vomiting, had headaches and hiccoughs. His blood pressure was 148/90. On the 6th and 7th hospital days he had tarry stools and coffee-ground vomitus, and voided only 180 cc. of urine. It was noted that his blood pressure was falling, but the actual values were not noted. On the 9th hospital day he had generalized convulsions and complete anuria and died on the next day.

**Laboratory Data.** The blood urea nitrogen rose from 17.9 to 83.3 mg. per 100 cc., the blood creatinine from 1.8 to 10 mg. per 100 cc., the uric acid from 7.6 to 8.2 mg.

per 100 cc. Six urine examinations showed a heavy trace of 4+ albumin. They were loaded with casts and white blood cells. The red blood count was 5.35 million, with 95% hemoglobin. The white blood count was 17,800 (87% polymorphonuclears, 10% lymphocytes, 2% monocytes, 1% eosinophils).

**Morbid Anatomy.** (N 1041.) The heart weighed 480 gm. The myocardium of the left ventricle was hypertrophied and the right chambers were dilated. The *pulmonary alveoli* were filled with fluid and many hemorrhagic areas were seen scattered throughout the lungs. Marked congestion was present. The liver weighed 1820 gm. Cloudy swelling and granular degeneration were present. The esophageal mucosa was deep red. There were linear gray escharotic lesions extending to the stomach. The mucosa was denuded in many areas. There was marked congestion, hemorrhage and round cell infiltration. The stomach showed many hemorrhagic areas. The *small intestine*, *cecum* and *sigmoid* showed extensive hemorrhagic lesions of the mucosa. A few pin-point hemorrhages were seen in both *kidney* cortices. On section, the cortex was pale and edematous. The pelves showed many hemorrhagic areas. Many of the kidney tubules showed desquamation of the lining cells and their lumina were filled with granular material. The brain showed congestion and edema and weighed 1210 gm.

In the right *adrenal* gland medulla there was a gray nodule about 1 cm. in diameter. This nodule was surrounded by compressed cortical tissue which varied in thickness, with connective tissue outside of it. In one area the capsule was fragmented and absent. In another area the medullary tissue reached the connective tissue capsule. Within the medullary tissue, the cytoplasm stained blue and appeared granular. In many areas the cell outlines were indistinct and most of the cells were stellate in shape. The nuclei were round and oval and vesicular. Distinct nucleoli were seen in most nuclei. Occasional mitotic figures were seen. The cells were arranged in small groups separated by delicate connective tissue. There were many blood-vessels distended with red blood cells.

**Anatomic Diagnosis.** Mercurial nephrosis; ulceration and hemorrhage in gastro-intestinal tract; parenchymatous hepatitis; pheochromocytoma of right adrenal gland.

CASE 5. J. F., a 61 year old white male, was first seen at this hospital 8 years before admission with epigastric pain, constipation, loss of weight and pallor. At this admission, he had Roentgen ray evidence of a duodenal ulcer. His blood pressure at that time was 90/70. During the 4 years before admission the patient had 4 normal electrocardiograms, 2 normal chest Roentgen rays, and his blood pressure on 5 occasions varied from 126/76 to 150/90. His chief complaints on admission were weakness and loss of about 100 pounds in 6 months. He also had pain in the epigastrium and in the right upper quadrant. This pain was not related to food or respiration. He had severe anorexia at the same time.

able 2 finger breadths below the right costal margin, and there was some fullness at the right side of the epigastrium.

*Course.* At operation on the 5th hospital day, subhepatic and subphrenic abscesses were seen and drained. On the 19th hospital day, the patient's wound was draining profuse purulent material. He became drowsy and disoriented and there was evidence of thrombophlebitis of the left leg. On the 29th day, he had chills and fever and it was noted that his general condition was poor. Thrombophlebitis was still present. On the 34th day, the patient did not void at all. He had a high fever, continued to go downhill, and died 4 days later.

*Laboratory Data.* Eight urine specimens

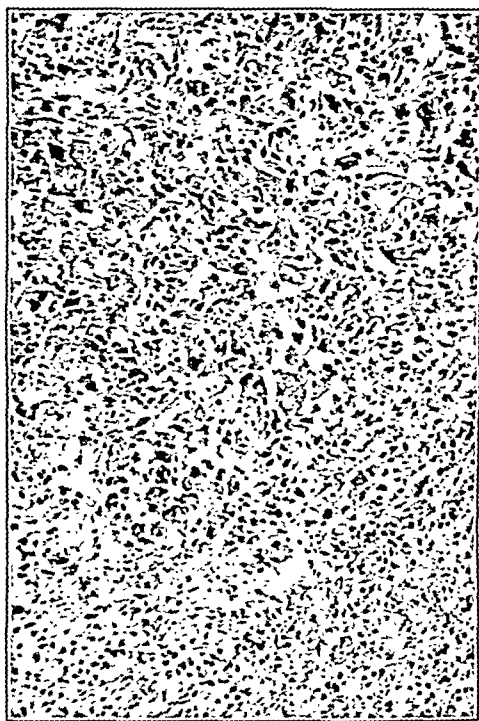


FIG. 7. Case 5. Photomicrograph of tumor in the adrenal gland. Note normal tissue at bottom. (H. and E.  $\times 100$ )

*Physical Examination.* On admission the patient's temperature was 102.6° F. pulse 110 per minute, and the blood pressure 118/70. He was a well-developed, poorly nourished, elderly white male showing pallor and loss of weight. There was pain and tenderness in the epigastrium and in the right upper quadrant. The liver was palp-

were not remarkable. The hemoglobin varied from 50 to 67%. The red blood count varied from 2.6 to 3.3 million cells. The white blood count varied from 13,000 to 26,000. The polymorphonuclears varied from 77 to 93%; the lymphocytes from 5 to 20%. The sedimentation rate was always between 125 and 137 mm. per hour. The

icterus index was 14.7 and 16. The blood sugar, urea, protein and A/G ratio were not remarkable. The patient's blood pressure during his hospital stay varied from 110/50 to 130/80.

*Morbid Anatomy.* (N43-137.) The *skin* was lemon yellow, and the scleræ icteric. There was a sinus tract opening at the upper part of the abdominal wound. Many adhesions were found in the abdomen and a large amount of creamy green yellow odorless pus was also seen. The *heart* showed some fatty infiltration. The *lungs* showed abscesses and fibrosis. The *esophagus* revealed chronic inflammation and there were ulcers in the duodenum, 1 of which perforated and showed a communication with the inferior surface of the liver. Between

groups, separated by delicate vascular connective tissue. The cytoplasm of the tumor cells was granular and stained light blue. The nuclei stained dark blue and varied greatly in size. Most of them were round and oval and vesicular. Nucleoli were seen in many nuclei.

*Anatomic Diagnosis.* Ulcers in duodenum with perforation; perihepatic and intrahepatic abscesses, wound of operation for; pylephlebitis; infarct in liver; icterus; abscesses in lungs with fibrosis; thrombophlebitis, external iliac, femoral and saphenous veins, left; anemia; congestion of viscera; arteriosclerosis, generalized; fatty infiltration in heart; esophagitis, chronic; nephrosclerosis; pheochromocytoma in adrenal gland, left; prostatitis, chronic with abscess.

TABLE 2.—BLOOD PRESSURE DURING HOSPITAL STAY (CASE 3)

Admission	2nd day	3rd day	4th day
184/86	192/90	220/90	226/90 220/102 220/104

the liver and the adherent diaphragm there was a moderate amount of creamy yellow green pus and a large collection of pus within the caudate lobe of the liver. There were abscesses and an infarct in the right lobe of the *liver*. The *kidneys* showed nephrosclerosis. There was a large organized thrombus in the left internal saphenous vein. *B. coli* and *Staph. aureus* were obtained on culture from these abscesses. The prostate also showed several small abscesses.

The right adrenal gland measured 6 by 3.4 by 0.8 cm. and weighed 6 gm. The left gland measured 6.2 by 3.5 by 1.1 cm. and weighed 8 gm. The external surfaces were discolored gray green. On section, the cortex and medulla were distinct. The left adrenal was the seat of a small circular nodule which on cross-section was pink in color and measured 0.8 cm. in diameter. Microscopically, both adrenal glands were not remarkable except for the small tumor mass arising from the medulla of the left adrenal gland. This nodule was almost entirely surrounded by compressed cortical tissue. In 1 area the nodule was seen to merge with normal medullary tissue. Within this mass the cells were arranged in small

Cases 4 and 5 never had hypertension, paroxysmal or sustained, so that the pheochromocytoma had no obvious clinical effect in these 2 cases. These 2 patients died of causes unrelated to their pheochromocytomata. Lazarus and Eisenberg<sup>13</sup> stated, "Paragangliomata are usually small and symptomless, as a result of which most of them have been found at autopsy." Moreover, the age of these 2 patients (40 and 61) was such that it cannot be said that they were in the early stage of the disease and that they would have developed symptoms if they had gone on long enough. This is particularly true in view of Case 2, of pheochromocytoma with a more or less typical story in a woman 34 years old. Thus, there is no indication that the symptomless lesions are earlier stages of the symptomatic ones.

**Summary and Conclusions.** A series of 5 cases of adrenal pheochromocytoma is presented as examples of the various clinical types of this tumor. They include (1) the malignant tumor with metastases, as in Case 1; (2) the benign tumor with



hypertension (paroxysmal) in Case 2 and sustained in Case 3; (3) the benign tumor with no signs or symptoms, found accidentally at autopsy, as in Cases 4 and 5.

The malignant variety is exceedingly rare. The case in this series is the ninth on record and the only one with metastases to the brain. Antemortem diagnosis and treatment of the malignant lesions give little promise of improvement, since the earliest signs are usually those of metastatic involvement. Moreover, the presence of metastases is the only reliable criterion of malignancy in these cases, since the histologic structure of the benign and malignant tumors is similar. The absence of hypertension in the patients with malignant lesions is unexplained. Perhaps the malignant cells lose the property of secreting the "pressor substance." We noted that the affinity of the primary and metastatic lesions for chrome salts was just as great as in the benign tumors.

The benign pheochromocytoma with paroxysmal hypertension is well recog-

nized today. However, in the group with sustained hypertension, great room for improvement in diagnosis exists. In these latter cases the diagnosis must always be kept in mind and definite effort made to rule it in or out. The use of the Roth-Kvale<sup>17</sup> histamine test or the benzodioxane test of Goldenberg *et al.*<sup>7</sup> may be important in this respect.

The benign pheochromocytomas without clinical signs and symptoms have little or no diagnostic significance at present. However, the presence of hypertension in some patients with benign tumors and its absence in others with the same lesion is unexplained. There is some indication that these symptomless lesions are not precursors of the symptomatic ones from the comparative ages of these patients. Moreover, the size of the tumor in Case 3 with sustained hypertension was approximately the same as in Cases 4 and 5 without hypertension, so that the presence of symptoms does not seem to depend on the size of the lesion.

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# AMYLOIDOSIS IN RHEUMATOID ARTHRITIS

## A Report of Ten Cases

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ON the basis of previous reports in the literature amyloidosis complicating rheumatoid arthritis is uncommon, and to date has been reported only 40 times, but there is reason to believe that the 2 conditions coexist more frequently. The fact that simultaneous occurrence was usually discovered at postmortem examination indicates a general lack of awareness of the association. Four additional postmortem and 6 living cases of amyloidosis occurring in patients with rheumatoid arthritis are now reported.

Trasoff, Schneeberg and Scarf<sup>9</sup> completely reviewed the literature up to 1943 and again focussed attention on the association of the 2 diseases. Since then 8 additional cases have been reported.<sup>3,4,7,9,11</sup> Review of the additional cases adds little to the conclusions reached by Trasoff, Schneeberg and Scarf.

**POSTMORTEM CASES.** The records of 58 patients with rheumatoid arthritis who came to postmortem study were reviewed to determine the incidence of amyloidosis. There were 4 cases in which amyloidosis could not be attributed to causes other than rheumatoid arthritis.

The arthritis in the group studied was severe. The duration varied from 11 to 23 years (Table 1). There was no obvious difference in duration or severity from

the non-amyloid group. Despite the presence of suggestive clinical evidence of amyloidosis, the Congo red test had not been performed in any of these cases, since the diagnosis was not suspected antemortem. Edema was present in 3 of the 4 cases, hepatosplenomegaly in 1 and hypo-albuminemia in all 3 cases in which the serum proteins were estimated. Unfortunately, hepatic and renal functions were not well studied in this group. The urine in all instances showed albumin, varying from a trace to 4+. None of the patients died in uremia, though the non-protein nitrogen was elevated in 1 and the blood urea nitrogen in another case.

The postmortem findings showed amyloidosis of varying severity and distribution, involving liver, spleen and kidney in every case, and, in addition, in 1 case the adrenals, pancreas and heart. Case 2 had a metastatic chorioepithelioma complicating the rheumatoid arthritis. The rapidity of the downhill course following the appearance of the tumor made it unlikely that the amyloidosis was in any way related to the occurrence of the tumor. The presence of rheumatic heart disease in 3 of the 4 cases is of interest.<sup>8</sup> Amyloidosis was not the immediate cause of death in any of the cases.

**LIVING CASES.** With these results in

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PERITENT CLINICAL AND LABORATORY FINDINGS

TABLE 1.—POSTMORTEM CASES OF RHEUMATOID ARTHRITIS AND			
Pertinent Clinical and Laboratory Findings			
	Case 1. A. E. 52 yrs. Male	Case 2. J. S. 34 yrs. Male	Case 3. P. W. 53 yrs. Female
Pathologic diagnosis	Rheumatoid arthritis; chronic rheumatic arthritis; amyloid- osis, liver, spleen, kidney	Rheumatoid arthritis; chronic rheumatic valvulitis; fibrous pericarditis; choriocarcinoma with metastases; amy- loidosis, liver spleen, kidney; acute pyelonephritis	Rheumatoid arthritis; pulmon- ary fibrosis; necrotizing bron- chiolitis, acute; chronic adhe- sive pericarditis; amyloidosis, liver, spleen, kidneys, adren- als, heart, pancreas
Duration of arthritis (yrs.)	18	14½/98	11
Physical examination:	110/80	2+ +	110/70
Blood pressure	2+ 0	+	0
Blood	0	1 018	0
Edeema	1 012	2+ Many RBC, WBC, casts	0
Spleen	2+	NPN 75	120/80
Liver	Many hyaline casts	3.0/2.7	1+
Kidney function:	17	162/68	0
Specific gravity	3.6/2.6	None	0
Albumin	—	2 8	1 020
Microscopic	—	44	Trace
BUN (mg. per 100 cc.)	3 8	18,600	Neg.
Liver function:	60	35-85	15 6
Albumin/globulin (gm. %)	15,200	Neg.	—
Cholesterol T/E (mg. %)	88-112	0	50/90
BSP % (30 min.)	Neg.	Neg.	Neg.
Hematology:	200	Gold	50
Red blood count	Neg.	Liver extract	3+
Hemoglobin (%)	Neg.		Typhoid vaccine
White blood count	Neg.		
ESR (mm./hr.)	Neg.		
Strep.—hemagglutins	Neg.		
Antistreptolysin	Neg.		
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TABLE 2.—LIVING CASES OF RHEUMATOID ARTHRITIS AND AMYLOIDOSIS

*Pertinent Clinical and Laboratory Findings*

	Case 1. R. S. 32 yrs. Male	Case 2. G. G. 50 yrs. Male	Case 3. J. M. 43 yrs. Male	Case 4. M. B. 39 yrs. Male	Case 5. M. W. 54 yrs. Male	Case 4. M. M. 54 yrs. Male
Clinical diagnosis . . .	Rheumatoid arthritis; rheumatic heart dis- ease, M.I.; amyloid- osis	Rheumatoid arthritis; duodenal ulcer; amyloidosis	Rheumatoid arthritis; pulmonary tubercu- losis, inactive; amy- loidosis	Rheumatoid arthritis; rheumatic heart dis- ease, M.I., MS, A.I; amyloidosis	Rheumatoid arthritis; rheumatic heart dis- ease, M.I., MS; amy- loidosis	Rheumatoid arthritis; rheumatic heart dis- ease, M.I., MS; Amyl- oidosis
History . . . . .	Gonorrhea 11 yrs. ago, cleared	...	Pulmonary Tb. regan 11 yrs. ago Inactive for 9 yrs.	Gonorrhea 10 yrs. ago		
Duration of arthritis (yrs.)	10	12	120/92 9	29	15	3
Physical examination:						
Blood pressure . . .	104/52	110/74	120/92	115/65-150/0	104/50	115/80
Edema . . . . .	4+	2+	0	1+	2+	2+
Spleen . . . . .	0	+	+	+	+	0
Liver . . . . .	0	+	+	+	+	+
Kidney function:						
Specific gravity . . .	1.019	1.023	1.018	1.017	1.029	1.019
Albumin . . . . .	4+	4+	4+	0-1+	3+	2+
Microscopic . . . .	Many hyaline casts	Many hyaline casts	Many hyaline casts	Neg.	Many hyaline casts	Neg.
BUN (mg. %) . . . .	16.6	13.9	NPN 38	12.0	11.4	15.7
Urea clearance (%) . .	126-39.2	70	70	45	52	55
PSP, % (1 hr.) . . .	12	18	15	—	35	37
Liver function:						
Albumin/globulin . .	1.6/2.1	2.7/3.2	3.8/2.9	3.9/2.9	3.9/2.4	3.5/2.6
Cholesterol T/E . . .	280/20	225/?	290/207	125/97	202/161	205/153
BSP, % (30 min.) . .	5	5	None	3	None	None
Cephalin flocculation	Neg.	Neg.	3+	Neg.	3+	Neg.
Amino acid N (mg. per 100 cc.) . . . . .	3.9	3.6	4.5	4.0	4.6	5.1
Hematology:						
Red blood count . . .	2.6	2.8	4.3	3.7	3.5	4.4
Hemoglobin (%) . . .	38	36	56	60	58	73
White blood count . .	12,800	8400	7000	6500	9400	9000
ESR (mm. per hr.) . .	29-74	30	60-120	34-108	20-85	22-96
Strep.—hemagglutins .	Neg.	—	—	—	—	—
Antistreptolysin . . .	—	—	250-500	833	333	166
Plasma volume . . . .	4.920	5.293	5.293	4.100	4.180	—
% Congo red absorption	100	95	93	86	86	81
Liver biopsy . . . . .	—	Amyloidosis	—	—	Amyloidosis	—
Therapy . . . . .	Typhoid vaccine, gold, Roentgen ray, sul- fonamides, malaria	Gold, Roentgen ray	Gold, pneumothorax	Gold, fever, Roentgen ray, sulfur, vitamin D, sodium thiosul- fate	Typhoid vaccine, sul- fur, gold, Roentgen ray, bismuth, liver extract, salicylates	Salicylates, vitamin C

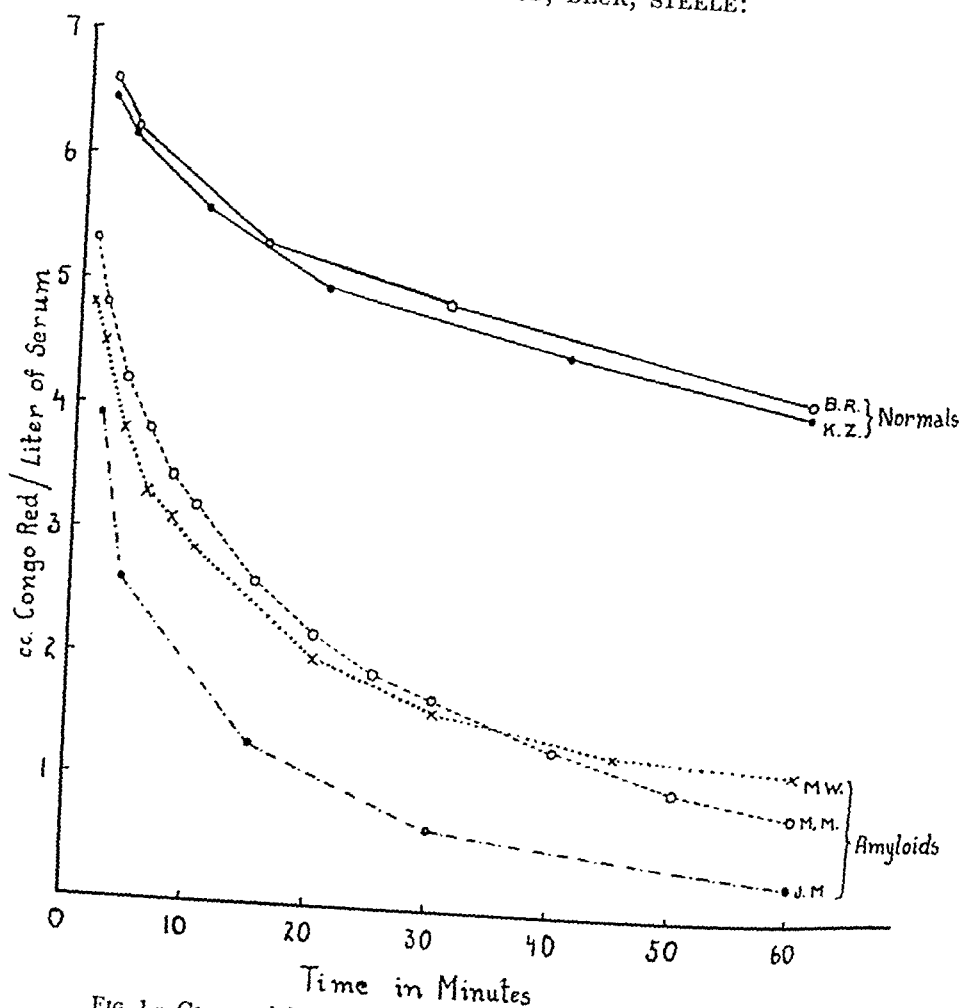


FIG. 1.—Congo red disappearance curve in normal and amyloid cases.

mind, a search for amyloidosis was made among the 56 living cases with rheumatoid arthritis. The patients were subjected to thorough study, including measurement of renal and hepatic function in all cases suspected of amyloidosis. The Congo red test as modified by Taran and Eckstein<sup>2</sup> from Bennhold's original method was used.<sup>2</sup> A Coleman junior spectrophotometer was used for the colorimetric comparison. The interpretation of the Congo red test depended as much upon the slope of the curve of disappearance as it did upon the absolute amount of dye absorbed (Fig. 1). Five of the 6 cases showed Congo red absorption ranging from 86 to 100% 1 hour after injection. In the remaining case, 81% of the injected

dye was removed after 1 hour. Wherever possible, liver biopsy was performed to confirm the clinical impression.

Amyloidosis was found in 6 patients (Table 2). The duration of the arthritis in this group ranged from 2½ to 29 years and was severe in all instances. It was no worse, on the average, than in many of the arthritics without amyloidosis of equal or longer duration. It appears certain that amyloidosis was secondary to rheumatoid arthritis in 5 of the 6 cases. The exception (Case 3) had tuberculosis that had been pronounced arrested and had remained so for 8 years. Clinical findings attributable to the amyloidosis appeared sometime after the tuberculosis had become arrested, at a time when his

rheumatoid arthritis was progressing rapidly.

Hepatosplenomegaly was present in 4 cases and hepatomegaly alone in 1. Five of the 6 patients showed peripheral edema of varying degree. Two of these 5 had serum albumin levels below 3 gm. The serum globulin was normal in all instances.

Albuminuria of varying degree was present in all of the patients. The only formed elements found in the urine were hyaline casts and white blood cells. There was some impairment of the ability to concentrate urine but nitrogen retention did not occur. Urea clearance was above 50% of normal in 5 of the 6 cases. Oddly enough, phenolsulfonephthalein excretion was markedly impaired in all patients.

Liver function was tested in all patients. The bromsulfalein test was normal in all cases. Two patients had a 3+ cephalin flocculation, 2 had hypoproteinemia with reversal of the albumin globulin ratio. The positive cephalin flocculation occurred in patients with normal serum proteins. Hypercholesteremia and hypoproteinemia were associated in 1 patient.

A finding of great interest was the definitely low serum amino acid levels in all of our living cases, varying from 3.6 to 5.1 mg. amino acid nitrogen per 100 cc. of serum (normal values 5 to 7 mg.). This might be referable, in the absence of controlled protein intake, to poor diet, poor absorption, increased loss of protein *via* the kidneys, but the possibility exists that a disturbance of protein metabolism in the liver may be the important factor.

Hematologically all cases showed moderately severe normocytic hypochromic anemia. Evidence of rheumatic cardiac involvement occurred in 4 of the 6 living cases.

**Comment.** As a part of a study<sup>10</sup> directed toward improving the accuracy of the Congo red test for diagnosis of amyloid disease, plasma volumes were studied in 5 cases, using T-1824 (Evans blue). The volumes obtained were much greater than those predicted on the basis of body

surface area (Table 2). Unusually rapid disappearance of the dye from the blood stream could give these results. Since T-1824 is a vital dye, it might be fixed by amyloid tissue in a fashion similar to Congo red. By staining sections of tissue with T-1824, it was found that amyloid tissue fixed the dye to a much greater extent than normal tissue. If phenolsulfonephthalein is also picked up by amyloid tissue, it would, of course, not be useful in the study of renal function in amyloidosis. That this state of affairs may exist is suggested by the fact that the phenolsulfonephthalein excretion test was quite low in these patients and not in accord with the results of the other tests of renal function. There is also a possibility that the failure to obtain abnormal retention of bromsulfalein in the blood stream, despite the extensive replacement of hepatic cells by amyloid deposition histologically, might be referable to a similar process.

Analysis of the data fails to show any difference in the severity and therapy between patients suffering with rheumatoid arthritis who developed amyloid disease and those who did not.

It appears that deposition of amyloid does not occur as rapidly in rheumatoid arthritis as in tuberculosis or chronic suppuration. The amyloid process *per se* was apparently not responsible for death in patients with rheumatoid arthritis. Earlier recognition of amyloidosis would permit testing the efficacy of the recently recommended therapeutic regimen of desiccated whole liver powder.<sup>5,6</sup>

**Summary and Conclusion.** 1. Four cases of amyloidosis were found among 58 autopsied cases of rheumatoid arthritis.

2. Six cases of amyloidosis were found among 56 living patients with rheumatoid arthritis.

3. The incidence of amyloidosis appears to be higher in rheumatoid arthritis than is generally believed.

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# ELECTROENCEPHALOGRAPHIC RECORDS IN RELATION TO BLOOD PRESSURE CHANGES IN ECLAMPSIA

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THIRTY-THREE electroencephalographic (EEG) records were obtained before, during, and after eclamptic convulsions in 9 cases. Special attention is paid in this paper to the changes in the EEG and the improvement in the clinical picture when the high blood pressure, which was associated with the toxemia, was lowered either through the use of a caudal analgesia, veratrum viride, or by allowing sufficient time to elapse for a normal drop in the blood pressure.

As the blood pressure was lowered after use of any of these methods, the convulsions ceased and the clinical picture im-

proved markedly. The EEGs were obtained in some cases before delivery and the blood pressure was lowered artificially; however, in others the EEGs were obtained following delivery, and whenever possible follow-up EEGs were obtained for 10 days following the delivery.

An earlier report by Whitacre *et al.*<sup>4</sup> gave a description of 1 case in which the EEG tracings were obtained at the same time the blood pressure was lowered through the use of a caudal analgesia. The 9 cases presented here represent a continuation of this study.

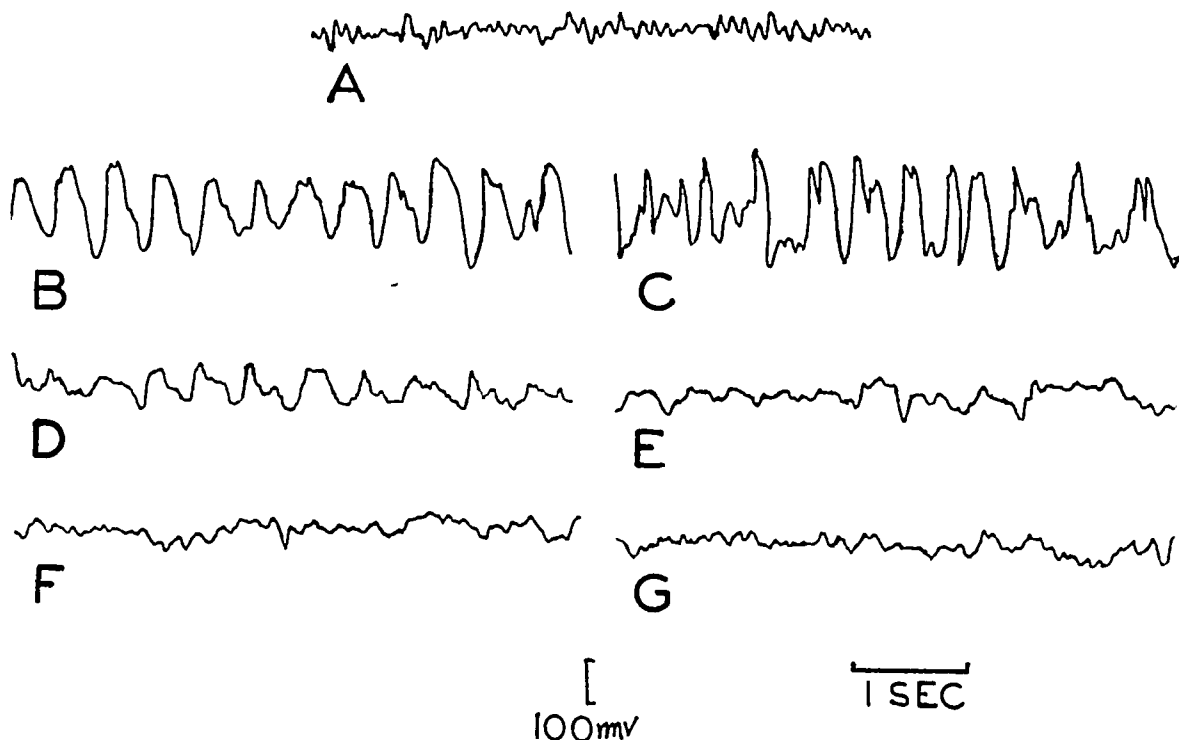


FIG. 1.—Electroencephalogram. Case 1. A, Record before delivery; blood pressure 145/100. B, Record on day following delivery. C and D, Record on same day when blood pressure was falling. E, Record on following day; blood pressure 140/120. F, Record 3 days after delivery. G, Record 6 days after delivery. (Poland Photogs.)

(\*) Study facilitated by grant-in-aid from Life Insurance Medical Research Fund.



**Material.** Three of the 9 cases have been selected as samples for special study since a large number of tracings were obtained and because they represent the whole group of cases. Bipolar (precentral to occipital leads) were used in all sample runs reported. Summaries of the remaining cases are given following the samples.

On the following day another EEG was obtained when the blood pressure was 140/120 (Record E). A continued increase in the low voltage fast material and a decrease in the high voltage slow activity is apparent. A sample of the record obtained the following day is given in Tracing F.

The final sample (Record G) was ob-

TABLE 1.—CASE 1

	Date (1946)	Time	B.P.
A.	Feb. 15	....	145/100
	Feb. 17	Baby delivered (caudal analgesia) (2 convulsions)	
	Feb. 18	11:30-11:40	172/108
B.	Feb. 18	3:20	165/122
C.	Feb. 18	4:30	156/120
D.	Feb. 18	....	140/120
E.	Feb. 19	....	130/102
F.	Feb. 20	....	100/70
G.	Feb. 23	....	

**CASE 1.**—The EEG records obtained on this case are presented in Figure 1. This case is an example of the changes in the EEG when no specific treatment was given to lower the blood pressure at the time the EEG tracings were obtained. The routine Dieckmann treatment for eclampsia was used.

This was a Negro girl, 15 years old, who was admitted to the hospital Feb. 15, 1946, with a slightly elevated blood pressure of 145/100 and a trace of albumin in the urine. An EEG tracing was obtained at this time (see Record A). At this time the EEG was essentially normal.

On the following day the blood pressure was 170/120 and a trace of albumin was found in the urine. The next day her blood pressure was 180/120, and the baby was delivered through the use of caudal analgesia, at which time the blood pressure was dropped temporarily to 120/70.

The day following delivery the blood pressure remained elevated at 170/120, and the patient had 2 convulsions. There was 2+ albumin in the urine. At this time an EEG was obtained which showed much high voltage slow activity. Records C and D were obtained the same day when the blood pressure was coming down. At 3:20 it was 165/122, and at 4:30 it was 156/120. It may be observed here that the slow high voltage waves were giving way to the faster low voltage material.

tained 3 days later. It should be noted in these last 3 records that there was a progressive change toward a more normal EEG. During this period of time the EEG had not completely returned to the preconvulsive level, but much improvement was shown.

**CASE 2.** A Negro girl, 19 years old. The EEG samples are presented in Figure 2. This case was selected for special study as an example of the effect of lowering blood pressure by the use of a caudal analgesia. The patient entered the hospital on Jan. 28, 1946, with a blood pressure of 170/100 and a trace of albumin in the urine. The patient had 3 convulsions before entering the hospital.

The first EEG was obtained on Feb. 9, 1946, the blood pressure ranging between 200/100 and 170/100, and the urine showed a 3+ albumin. Records A through F were obtained before and during the administration of a caudal analgesia, at which time the blood pressure was lowered from a high of 170/112 to a final stabilized level of 120/80.

Record A was obtained at 11:55 A.M. at which time the blood pressure was at its highest point. Thirty-eight cc. of metycaine was administered, and at 12:17 P.M. the blood pressure was 164/120. Much of the slow activity is still shown in the EEG (Record B).

Record C was obtained at 12:16 after an injection of 20 cc. more of metycaine

and the blood pressure had been lowered to 150/100.

Records D, E and F show the changes in the EEG as the blood pressure was lowered from 150/100 to 100/70 and stabilized at 120/80. It should be noted that as the blood pressure was lowered, more fast activity was observed and the slow waves, associated with the high blood pressure, were not found.

The baby was delivered later this same day by a low cervical Cesarean section. Records G, H and I were obtained in the 2 weeks following the delivery of the baby.

Record G was obtained the day after delivery, when the blood pressure was 190/120. It should be noted here that the high slow material, characteristic of the control run 2 days earlier, predominates.

Nine days after this run, Record H was obtained, at which time the blood pressure was 158/115. Nearly all of the slow activity had disappeared and fast low voltage waves were observed. The final record (I) was obtained 3 days later, at which time the blood pressure was 154/114, and the EEG was showing a return to a relatively normal pattern.

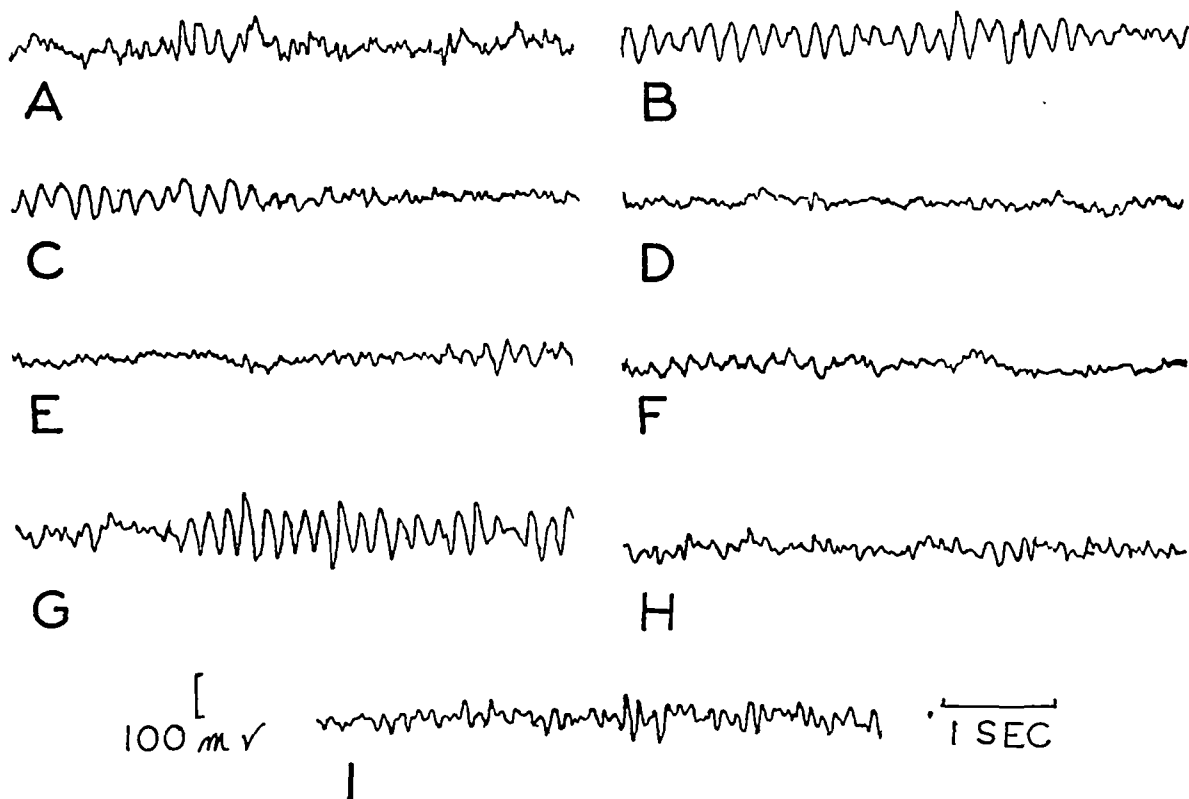


FIG. 2.—Electroencephalograms. Case 2. For details see text and Table 2.

TABLE 2—CASE 2

	Date (1946)	Time	B.P.	Caudal level
A.	Feb. 9	11:55	170/112	0
	38 cc. 1.5% metycaine hydrochloride			
B.	Feb. 9	12:07	164/120	0
	50 cc. 1.5% metycaine hydrochloride			
C.	Feb. 9	12:16	150/100	0
D.	Feb. 9	12:20	140/100	T 8
E.	Feb. 9	12:38	100/70	T 6
F.	Feb. 9	12:45	120/80	T 6
	Baby delivered Feb. 10, 1946			
G.	Feb. 11	..	190/120	0
H.	Feb. 20	..	158/115	0
I.	Feb. 23	..	154/114	0

CASE 3. A Negro girl, 21 years of age, was admitted to the hospital on June 22, 1946, with a blood pressure of 210/155, and the urine showed a 3+ albumin. This is an example of the use of veratrum viride as a method of lowering the blood pressure and the resulting changes in the EEG (Fig. 3).

The patient was brought to the EEG room while having a convulsion and the veratrum viride was used to lower the blood pressure. Record A in Figure 3 was obtained at 11:16 A.M. on this date in an inter-convulsive state. The blood pressure was 200/140. At 11:20 A.M., 0.5 mg. of veratrum viride was administered.

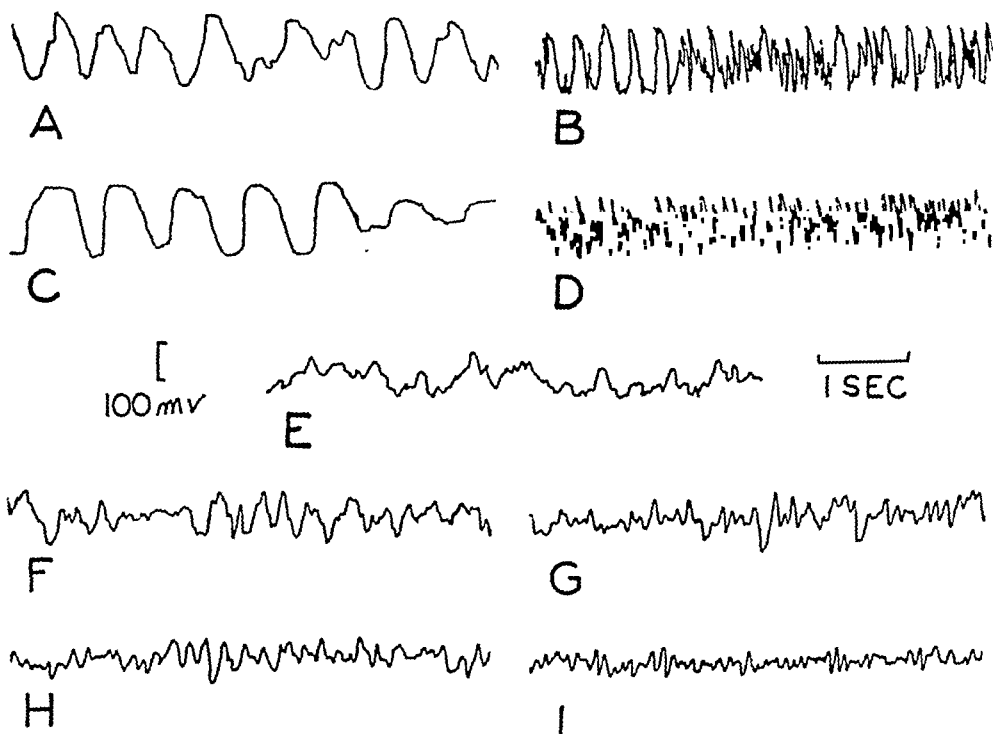


FIG. 3.—Electroencephalograms. Case 3. For details see text and Table 3.

TABLE 3—CASE 3

	Date (1946)	Time	B.P.
A.	June 22	11:16	200/140
		11:20	
		(0.5 mg. veratrum viride)	
B.	June 22	11:28	200/140
		(seizure)	
C.	June 22	11:30	205/108
		(interseizure)	
		11:32	
		(0.4 mg. veratrum viride)	
D.	June 22	11:45	160/110
		11:47	
		(0.4 mg. veratrum viride)	
E.	June 22	11:58	140/85
	Baby delivered June 24, 1946		
F.	June 26	...	140/110
G.	June 27	...	150/110
H.	June 28	...	132/110
I.	July 2	...	120/90

Record B was obtained during a convulsion at 11:28 A.M. at which time the blood pressure was still 200/140. The interseizure pattern is shown in Record C when the blood pressure was 205/108. At 11:32, 0.4 mg. more of veratrum viride was administered. Record D was obtained approximately 15 minutes later during another convulsion. The blood pressure was 160/110. At 11:47 A.M. another 0.4 mg. of veratrum viride was administered and the blood pressure further lowered.

A sample of the final EEG tracing in this examination is shown in Record E at which time the blood pressure was 140/85. It should be noted here that the high voltage slow waves were suppressed and some fast low voltage activity was appearing.

The baby was delivered 2 days later, at which time a caudal analgesia was administered and the blood pressure lowered from the initial 170/120 to 100/55 for a period of 1 hour. Record F was obtained 2 days after delivery, at which time there was still a marked dysrhythmia.

Records were also obtained 3 days after delivery (G), 7 days later (H) and 9 days later (I). During this time the EEG changes were from those typical of grand mal epilepsy and the interconvulsive state, to a relatively normal pattern. The clinical picture improved similarly.

CASE 4. This patient was admitted to the hospital Feb. 7, 1946, with a blood pressure of 144/100. The baby was delivered the same day, and immediately following delivery convulsions occurred. An EEG was obtained at this time which showed complete dysrhythmia from the whole cortex, with continuous spiking localized on the right side. The patient was comatose during most of the run and had left-sided as well as generalized convulsions. The patient died a few hours later. On autopsy a hemorrhage was found involving the right internal capsule and extending into the right ventricle. All the ventricles were filled with blood but only a few patches of blood were found in the subarachnoid space. It was noted on the autopsy report that a possible cause of the death may be on the basis of toxemia in pregnancy.

CASE 5. This patient was admitted to the hospital on April 1, 1946, with a blood pressure of 170/120 and a 1+ albumin in the

urine. An EEG record was obtained before delivery, during which time caudal analgesia was administered and the blood pressure lowered from the initial 170/120 to 100/55 during a period of approximately 1 hour. The EEG changes were from those typical of grand mal epilepsy and the intraconvulsive state to a relatively normal pattern. The clinical picture improved similarly. Records obtained on the day following, 7 days later, and 9 days later, showed continual improvement of the EEG as well as lowering the blood pressure and alleviation of symptoms.

CASE 6. The patient was admitted to the hospital on March 21, 1946, with a blood pressure of 175/140. In this case the EEG records were obtained only at times when the blood pressure was not lowered through the use of either veratrum viride or caudal analgesia. The EEG obtained on the 1st day of admittance was dysrhythmic from all areas, showing slow and fast high voltage mixed activity. Two days later the blood pressure was 150/122 and no improvement in the EEG record was observed. Ten days later the blood pressure was still slightly elevated (140/114). The urine showed a 3+ albumin and the EEG showed a very slight improvement on the earlier runs, but was still dysrhythmic.

CASE 7. The patient was admitted to the hospital on March 13, 1946, with a blood pressure of 190/130 and a 1+ albumin in the urine. The EEG records which were obtained at this time showed gross dysrhythmia in the form of high voltage slow and fast material. Delivery was the following day. On March 14, another EEG was obtained and the blood pressure was 150/90, which showed marked improvement over the earlier run, much of the record being relatively normal.

CASE 8. This patient was admitted to the hospital on May 10, 1946, with a blood pressure of 170/110. Delivery occurred that day, and 3 days later the patient had 2 convulsions. At this time the blood pressure was 146/100 and a 3+ albumin was found in the urine. The EEG at this time showed the continuous fast high voltage activity with some mixed slow material in all leads. Another EEG was obtained 7 days later, at which time the blood pressure was still elevated (140/105) and there was a trace

of albumin in the urine. This EEG showed some improvement over the earlier run, but it was still not completely normal, showing high voltage beta waves and spiking activity.

CASE 9. The patient was admitted to the hospital on April 26, 1946, with a blood pressure of 220/145 and a 2+ albumin in the urine. An EEG was obtained at this time which showed dysrhythmia from all areas, high voltage spikes, beta and slow components. The blood pressure was lowered to 82/60 through the use of caudal analgesia and a slight improvement was observed in the EEG. Six days later the blood pressure was still elevated to 180/120 and the EEG showed little or no improvement over the earlier run and the clinical improvement was slow.

**Discussion.** The findings of this study may be summarized as follows: 1. Changes in the EEG were associated with a drop in blood pressure, irrespective of

what caused this change in pressure. Slow high voltage activity was replaced by the more normal low voltage fast material.

2. Where the blood pressure did not change, the EEG did not improve.

3. Convulsions appeared to be controlled by the drop in blood pressure.

4. Clinical improvement was observed with drop of blood pressure and change in EEG pattern.

Indirect evidence is available which indicates that one factor which may play an important part in the changes described above is that of angiospasm or increased peripheral resistance.

Studying the pial blood-vessels in curarized cats through a window while recording brain volume simultaneously with blood pressure, Barrow, Green, Davis and Garol<sup>1</sup> observed dilatation of blood-vessels associated with low voltage fast EEGs after sponging the cut end of the nerve carrying parasympathetic impulses to the brain. With hyperventilation, fibrillation of blood-vessels was likewise observed, apparently concomitant with rhythmic electrical activity, and paling and constriction appeared related to high voltage activity of the brain. Such methods of

observation, however, did not permit satisfactory demonstration of exact temporal correspondence.

Darrow and Graf<sup>2</sup> attempted to obtain more conclusive evidence on the correspondence of EEG and vasomotor activity in identical or immediately adjacent regions of the brain. In a study on cats, a cranial window was prepared. Bipolar electrodes for recording the EEG were inserted through the glass window to enable microscopic observation of the cortex near the tip of the electrodes. The window was so constructed that the glass plate containing the electrodes could be slipped around over the frame to permit contact of the electrodes with various points on the exposed cortex. The plate was held in place by a superimposed ring which exerted pressure when laterally placed conical screws were tightened. Microscopic observation of brain and blood-vessels at the point of electrode contact and the surrounding area was possible. A more objective method of study, permitting recording of observations in parallel with the recording of the EEG, was obtained by the use of a Pulfrich photometer.

In this study, electrocorticogram, EEG, and electrocardiograph recordings were made. In general, they found a tendency for increase of frequency, increased potential of fast waves, and decrease of slow activity to be associated with vasodilatation, and that vasoconstriction gave the opposite, that is, increased potential of slow waves and a decreased fast activity. These general results were found in studies with ether asphyxia, hypercapnia, atropine and pilocarpine. During the experimental work, several animals developed convulsions of the grand mal type. Spindles in the EEG were observed to be associated with waves of constriction passing along the arteries, giving them the resemblance of sausage links.

In this study the workers did not record systemic blood pressure which was obtained in the earlier study.<sup>1</sup> However,

it might be assumed that with the blanching of the cortex and change in the caliber of the arterioles, there was probably a rise in blood pressure due to changes in peripheral resistance.

Generalization from studies done on animals applied to those on human subjects must, of course, be cautious, because of the large number of factors which differentiate the 2 groups. There is, however, a relatively clear parallel between the findings on animal material and those obtained from the eclamptic patients in this study. It is suggested here that perhaps one of the main factors in convulsions due to eclampsia may be angiospasm. Ophthalmoscopic examinations were not made on these patients. However, this will be done in a continuation of this study.

It is apparent that a great deal more work is necessary before conclusions can be drawn as to the part played by peripheral resistance in the convulsions of eclampsia. It is suggested, however, that angiospasm may play an important rôle.

With the coöperation of Dr. T. S. Hill, Professor of Psychiatry, and Dr. Frank Whitacre, Professor of Obstetrics and Gynecology. The author is also indebted to Dr. Robert A. Hingson and Dr. H. Charles Franklin, who administered the caudal analgesia, and Dr. Walter Loeb, who assisted in the selection of cases and carrying through of the clinical procedures.

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**Summary.** Thirty-three EEG records were obtained before, during and after eclamptic convulsions in 9 cases. Special reference is made to the improvement in the EEG tracings and clinical picture when the blood pressure is lowered either through the use of caudal analgesia, veratrum viride or by merely allowing sufficient time to elapse. Samples are given of each method and the resulting changes. The following factors were shown: 1. Changes in the EEG were associated with drop in blood pressure, no matter what caused the drop. Slow, high voltage activity was replaced by the more normal low voltage faster material.

2. When the blood pressure did not change, the EEG did not improve.

3. Convulsions were controlled by the drop in blood pressure.

4. Clinical improvement was observed with the drop in blood pressure and the improved EEG pattern.

5. It is suggested that perhaps angiospasm played an important rôle in the eclamptic convulsions.

# ADMINISTRATION OF MASSIVE DOSES OF VITAMIN P HESPERIDIN METHYL CHALCONE\*

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IN the early studies of Szent-Györgyi and co-workers<sup>1</sup> (1936), the designation vitamin P was applied to the group of flavones present in extracts of paprika and lemon peel, which appeared to restore abnormally increased permeability of capillaries. From citrin Mager<sup>13</sup> later isolated eriodictyol rhamnoside, and Higby<sup>10</sup> studied a number of relatively crude flavone preparations and concluded that the eriodictyol glucosides could not be the source of vitamin P activity. Pure hesperidin, pure limonin and pure eriodictyol had no effect on either blood pressure or capillary permeability, but the water-soluble yellow pigment from crude orange hesperidin was found to be active. This was identified as hesperidin chalcone, an unstable derivative, which on methylation was stabilized without affecting its vitamin P activity.

The clinical effect of vitamin P substances has been controversial, and information has been based largely on observations of the petechial index, as measured by the Göthlin test or one of its modifications, and by Scarborough's<sup>15,16</sup> modification of Hecht's<sup>19</sup> negative pressure method. These methods provide at best only crude approximations, as there are several known factors which influence the results and, furthermore, the positive and negative pressure methods do not give comparable results in the same individual. Bell *et al.*<sup>4</sup>

tested 142 healthy medical students by the negative pressure method and found low correlation in results, although the tests were consistent within themselves. Beaser, Rudy and Seligman<sup>3</sup> used several methods and concluded that all negative pressure methods were unreliable. Nevertheless, most animal and clinical studies indicate that vitamin P has a definite influence on capillary permeability as distinguished from the capillary lesion in scurvy (increased fragility) which responds to ascorbic acid.

Among the tests for capillary permeability is that described by Landis,<sup>11</sup> and later criticized by Bing,<sup>5</sup> who followed the same technique as Eppinger,<sup>7</sup> and Szent-Györgyi,<sup>1</sup> using a low pressure of 40 mm. Hg. The patient lies for  $\frac{1}{2}$  hour with arms horizontal, then the cuff is inflated (in this instance to 40 mm. Hg), and after  $\frac{1}{2}$  hour, blood samples are taken from each arm simultaneously and hematocrit and blood protein estimations made. The filtration rate ( $x$ ) is then determined by a

formula:  $x = 100 - 100 \frac{C_1}{C_2}$ , where  $C_1$  and  $C_2$

$C_2$  are the percentile blood volume from the unconstricted and constricted arms, respectively. Bing believed that the experimental error in this procedure was so great that it compromised the results. However, Landis had already stated that

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very low congestive pressures were unaccompanied by any changes great enough to permit conclusions, while at pressures of 80 mm. Hg or more, the capillary wall becomes relatively permeable to fluid. Plass and Rourke<sup>14</sup> applied pressures midway between diastolic and systolic and noted petechial areas below the arm band, accompanied by blood dehydration and an increase in plasma proteins.

Little is known about the absorption, utilization and excretion of vitamin P. The methods for quantitative measurement in body fluids are non-specific. Armentano *et al.*<sup>2</sup> found citrin and eriodictyol to be excreted in the urine and recovered about 50% following intravenous doses of 50 to 100 mg. Gero<sup>8</sup> administered epicatechin orally and observed maximum excretion in 1 hour which then fell rapidly by the end of 3 hours. Only 20% of the dose was recovered. Wilson and co-workers<sup>17</sup> developed a colorimetric test, using borocitric reagent, which appeared to be more specific for materials containing flavones similar in structure to quercetin, and amounts of citrin as low as 2 or 3  $\mu$ g. could be detected. Flavone determinations were carried out on plant tissues, but no flavone was detected in rabbit liver. The procedure seemed suitable for determination of excretion rates, however, since hesperidin methyl chalcone could be quantitatively recovered following the addition to the urine.

Since the acute toxicity of hesperidin methyl chalcone in mice, both when given orally and intravenously, was found by Chen<sup>16</sup> to be very low and there was no evident chronic toxicity in rats, it seemed expedient to determine whether administration of massive doses of hesperidin methyl chalcone would provide more specific evidence of clinical effect on capillary permeability, as measured by repeated determinations of differences in blood concentrations before and after constriction, and to determine what levels of dosage were required to provide saturation of patients as determined by the excretion of the substances in the urine.

With the exception of Cases J. E. (malignant hypertension) and K. H. (cirrhosis and Banti's disease), the patients chosen for study were in the main from a large group of diabetics showing retinopathy and, as a rule, grossly abnormal petechial indices, as measured by the modification of the Göthlin test described by Lewis, Schneider and McCullagh.<sup>12</sup> The blood pressure cuff was applied to the lower portion of the upper arm, inflated to diastolic level, and allowed to remain 3 minutes. Blood samples were drawn before and after constriction. The petechiae were counted in a 1 inch circle in the antecubital area. Capillary permeability was considered to be increased if more than 20 petechiae were present. In many instances they have consisted of showers over the whole extremity, far too numerous to count.

Observations were made at intervals ranging from 3 days to a week as ascending doses of hesperidin methyl chalcone were administered. Doses as large as 15 gm. were administered orally. Urine blanks of 24 hour samples were first determined, while the patients were kept under observation for several days until the controls showed that no interfering substance was present, and in order to approximate an average normal excretion from natural sources.

**Method of Determination in Urine.** The procedure of Wilson, Weatherby and Bock<sup>17</sup> depends on the formation by boric acid under anhydrous conditions, of a yellow complex with substances containing the flavone grouping. This color is greatly potentiated by citric acid. Recovery of hesperidin methyl chalcone (water standard) added to urine was found to be 99.6% of the theoretical amount.

**Results.** Figures 1 to 5 are derived from the clinical and laboratory numerical data plotted in % variation of concentration, which presumably should reflect differences in capillary permeability.

With the exception of Case A. W., there was an apparent decrease in capillary permeability as reflected by diminished per-



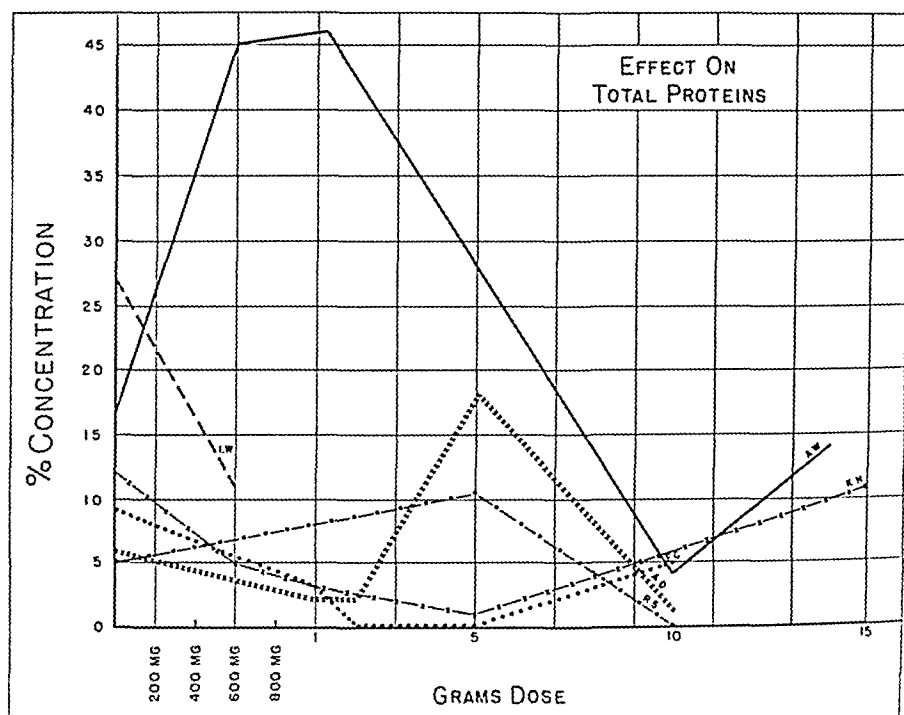


FIG. 1.—Effect of dosage increases on % concentration of total proteins after 3 minutes constriction at diastolic pressure.

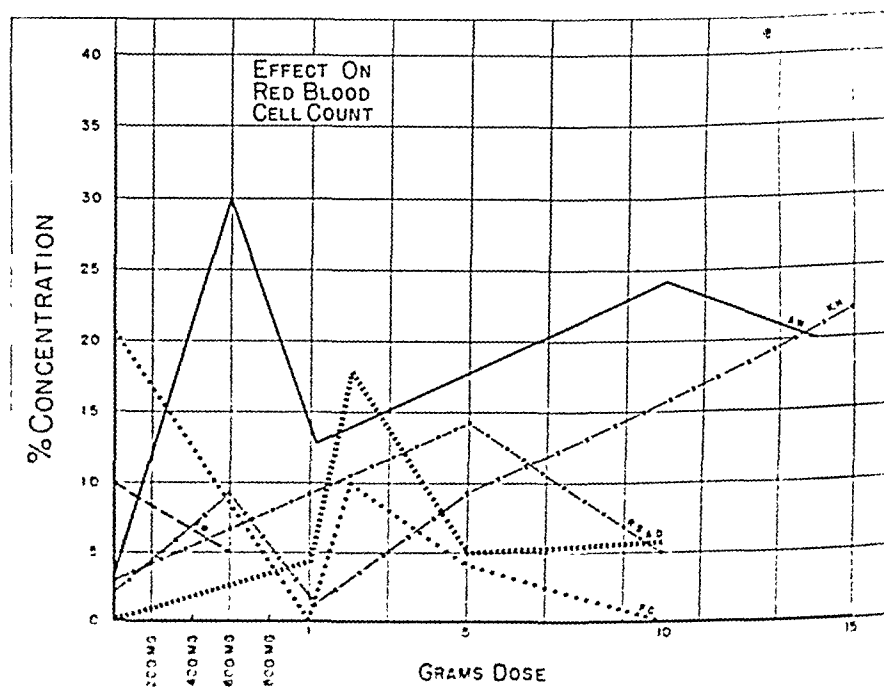


FIG. 2.—Percentage variation in red blood cell count following constriction.

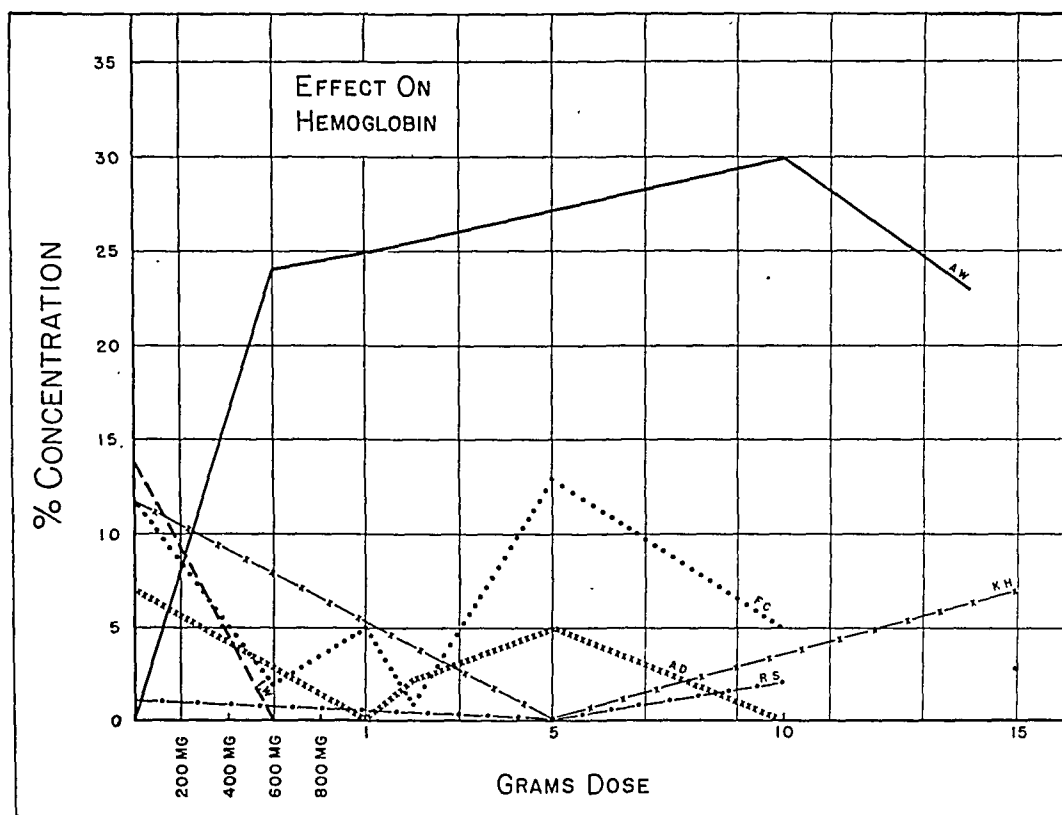


FIG. 3.—Initial apparent reduction in percentage concentration of hemoglobin after constriction followed by reversal of effect as higher dosages reached. Note opposite behavior of Case A. W.

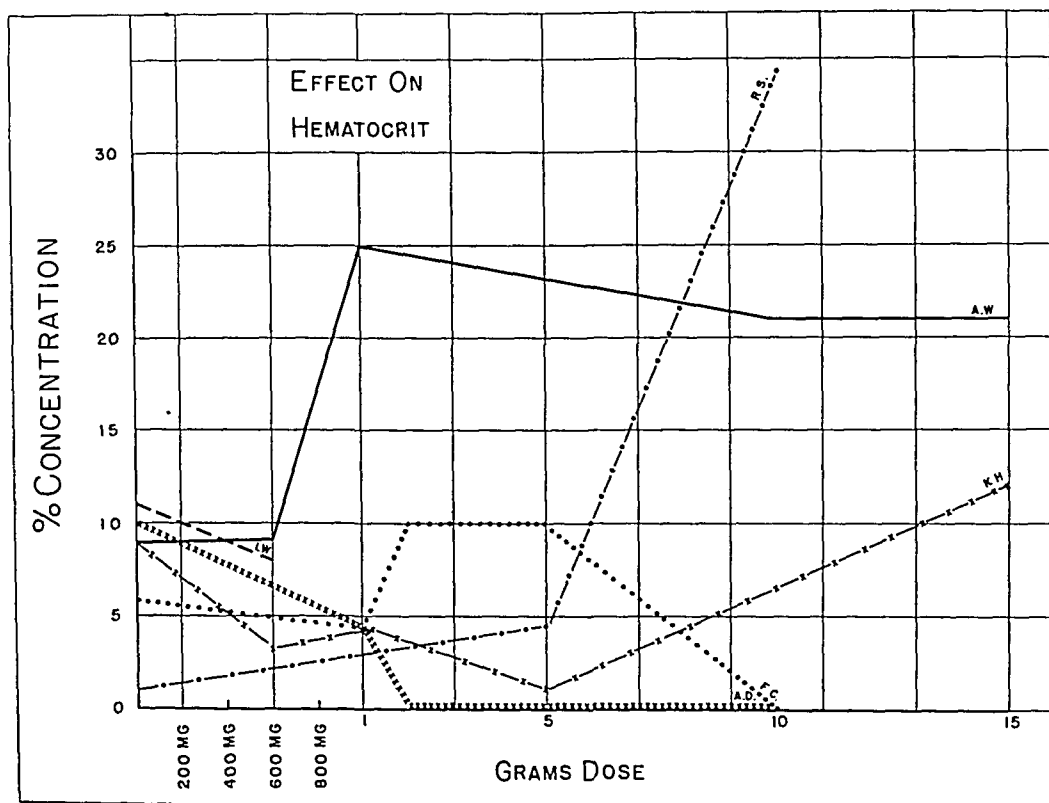


FIG. 4.—Changes in hematocrit after constriction, plotted as % concentration.

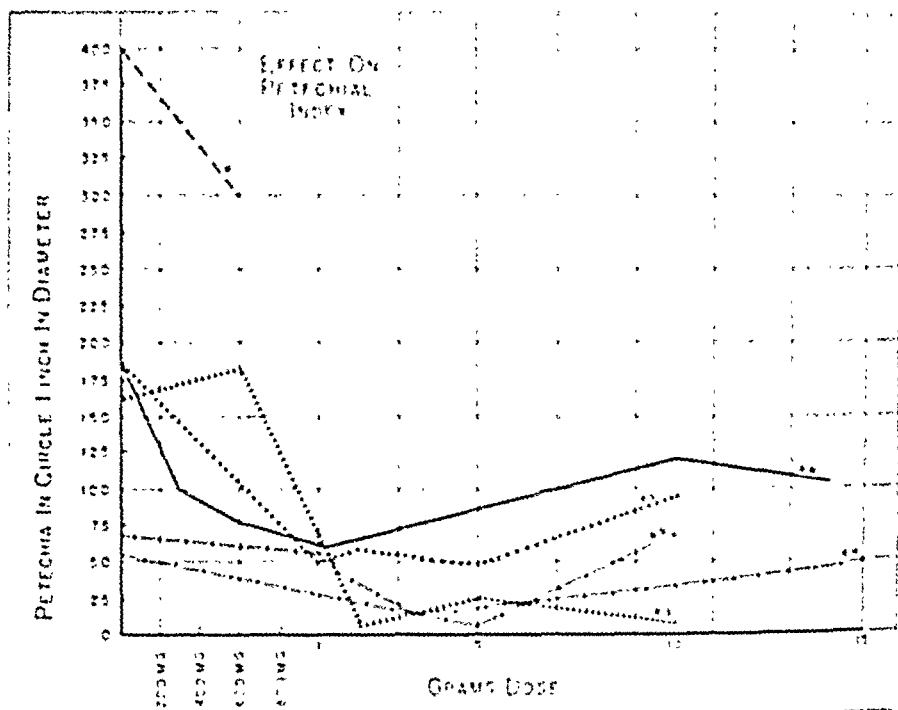


FIG. 5.—Initial reduction in number of petechiae following administration, followed by apparent loss of effect from larger doses.

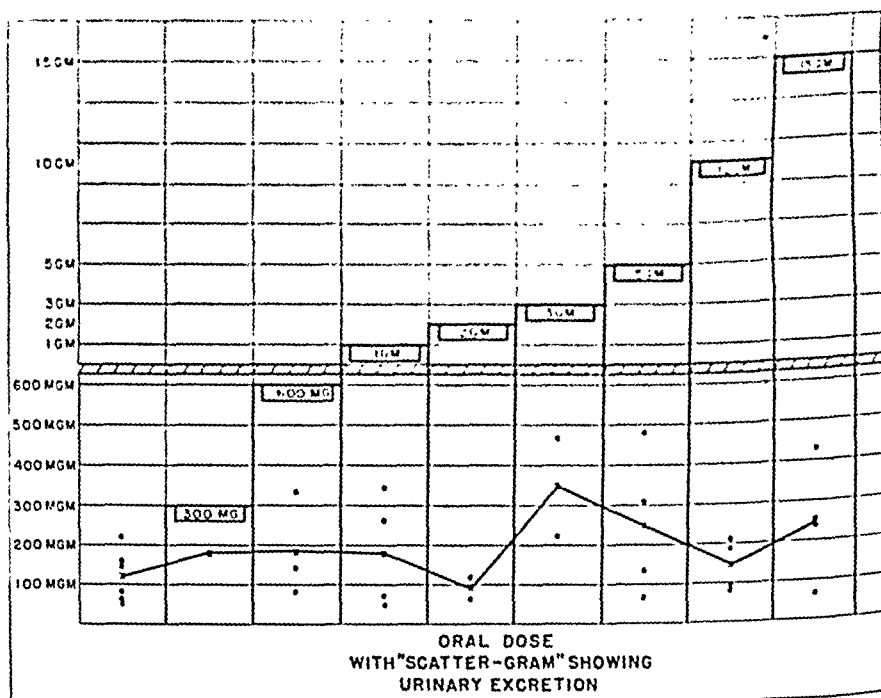


FIG. 6.—Excretion of hesperidin methyl chalcone in urine. There was no quantitative relationship between size of dose and quantity of drug recovered from the urine.

centage concentration of blood proteins as dosage of hesperidin methyl chalcone was progressively increased (Fig. 1). This was followed by a reversal of effect as doses of the order of 5 gm. or more daily were reached. Case A. W. behaved in a strikingly opposite manner. Similar results were observed in the determinations of erythrocyte concentration (Fig. 2), hemoglobin (Fig. 3), and hematocrit (Fig. 4). Only in effect on the petechial index (Fig. 5) was Case A. W. at all typical, and as shown in all the figures the variability of the changes was considerable. The effect on petechial index was the most constant finding, but in this respect also the initial reduction in petechial counts was not regularly maintained as dosage of the drug was progressively increased to levels as high as 15 gm. per day.

The excretion rates of hesperidin methyl chalcone in the urine were disappointing, in that the total quantities recovered were low and bore no quantitative relationship to the quantity of drug administered (Fig. 6).

The total lack of evidence of toxicity following these large doses is noteworthy. One patient stated that it increased the appetite. There were no significant effects on blood pressure, pulse or respiration. Only in one case was hesperidin methyl chalcone administered other than orally. This patient, J. E., age 32, having malignant hypertension, was given 300 mg. intravenously. There was a sharp fall in blood pressure, obvious dyspnea, and complaint of a "bitter taste" in the mouth.

Thanks are due to A. Lee Caldwell and J. Q. Bellard, for earlier work on the excretion of hesperidin methyl chalcone in animals; to T. Woodmansee, for the adaptation of the borocitric method to clinical usage; and to the Resident Staff of the Lilly Laboratories for Clinical Research, for their coöperation in making the clinical determinations.

The petechial index of 200+ was not altered.

**Discussion.** It is obvious that these methods fail to establish adequately the effect of hesperidin methyl chalcone on capillary permeability. The changes in concentration of blood proteins, erythrocytes, hemoglobin, hematocrit and petechial index are too variable to be statistically significant. The rather prompt effect on blood concentration which was usually noted and the failure to maintain it suggest the possibility of a tachyphylactic phenomenon, and negate the possibility that doses larger than those that have ordinarily been administered might be more efficacious. This is a curious effect, if indeed the active substance is a vitamin.

Lack of quantitative recovery of hesperidin methyl chalcone in the urine is also of interest. Either the drug is largely destroyed before or during absorption, or it may be utilized, or altered, or conjugated in some manner so that it escapes detection by the test employed.

**Conclusions.** 1. Studies of blood concentration by estimation of changes in total proteins, hemoglobin, red blood cells and hematocrit before and after constriction are not adequate to determine the effect of hesperidin methyl chalcone on capillary permeability.

2. The drug is not excreted in the urine as such.

3. Hesperidin methyl chalcone has been non-toxic in doses up to 15 gm. daily.

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# A SURVEY OF THE TREATMENT OF PERNICIOUS ANEMIA IN RELAPSE:

- (A) A COMPARISON OF THE HEMATOPOIETIC RESPONSE TO LIVER EXTRACT AND FOLIC ACID (L-CASEI FACTOR).
- (B) LIMITATIONS OF THE RETICULOCYTE RESPONSE AS A MEASURE OF ANTI-PERNICIOUS ANEMIA POTENCY.

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Since synthetic folic acid (*L-casei* factor) became available for general clinical use, several investigators have shown that this newest member of the vitamin B Complex is an active hematopoietic agent for the treatment of megaloblastic anemias. During the past two years, a number of patients with pernicious anemia in relapse have been treated with folic acid, and, as might well be expected, there has been considerable difference of opinion as to its efficacy in the treatment of this disease. It is established that folic acid is a very active hematopoietic agent and is effective in regenerating the blood elements in persons having a megaloblastic type of anemia. It is also certain that folic acid does not prevent or control the central nervous system changes commonly seen in pernicious anemia.

This brief paper has three objects in view:

- (1) To make a comparison of the

efficacy of folic acid and liver extract in the treatment of pernicious anemia in relapse.

- (2) To show the extreme variations in the magnitude of the reticulocyte response encountered in the treatment of pernicious anemia in relapse.

- (3) To indicate the limitations of the reticulocyte peak as a "yardstick" in the potency evaluation of anti-pernicious anemia preparations.

Due to the multiplicity of methods used for the determination of hemoglobin, it has seemed best not to present these data. Observations will be limited to data on erythrocyte regeneration and the magnitude of the reticulocyte response.

From our laboratory records\* it has been possible to collect complete data for 80 unselected cases of pernicious anemia in relapse treated with parenteral liver extract (of our own manufacture); from several investigators\*\*,

\* The author is indebted to: Dr. William P. Murphy, Peter Bent Brigham Hospital, Boston; Dr. J. E. Connery, Third Medical Division, Bellevue Hospital, New York; Dr. William B. Castle, Thorndike Memorial Hospital, Boston; Dr. William Dameshek, Boston Dispensary and Dr. Leo Meyer, Kings County Hospital, Brooklyn, for the data on patients (pernicious anemia in relapse) treated with liver extract.

\*\* The following investigators have very kindly supplied data on patients (pernicious anemia in relapse) treated with folic acid: Dr. Luis Amill, St. Luke's Hospital, New York; Dr. William B. Castle, Thorndike Memorial Hospital, Boston; Dr. William Dameshek, Boston Dispensary, Boston; Dr. William P. Murphy, Peter Bent Brigham Hospital, Boston; Dr. Joseph F. Ross, Evans Memorial Hospital, Boston; Dr. Carl V. Moore, Barnes Hospital, St. Louis; Dr. Byron E. Hall, Mayo Clinic, Rochester, Minnesota; Dr. John S. Lawrence, Strong Memorial Hospital, Rochester, N.Y.; Drs. William J. Darby, Edgar Jones and Henry F. Warden, Vanderbilt Hospital, Nashville; Dr. Philip Wagley, Johns Hopkins Hospital, Baltimore; Dr. Grace Goldsmith, Charity Hospital, New Orleans; Dr. David Miller and Dr. William H. Chapple, Edward J. Meyer Memorial Hospital, Buffalo; Dr. M. M. Wintrobe and Dr. G. E. Cartwright, Salt Lake General Hospital, Salt Lake City.

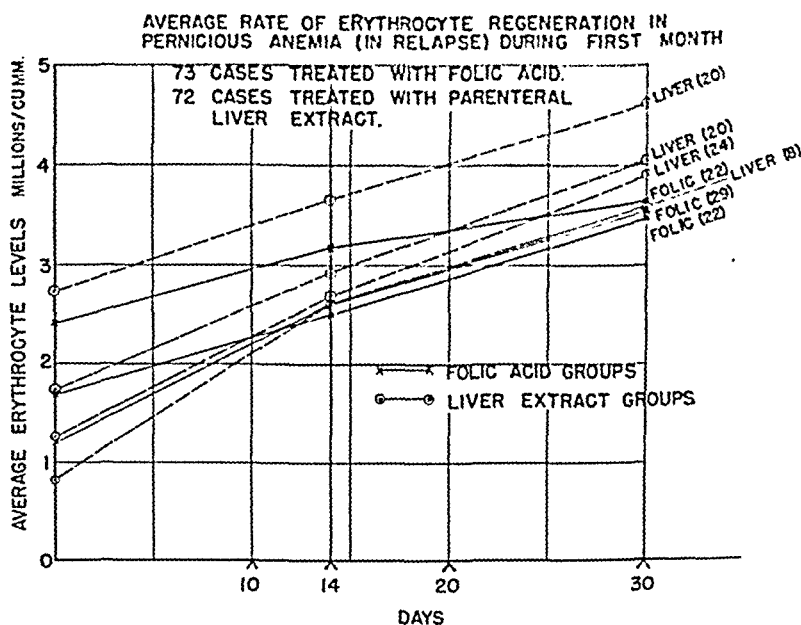
complete data on 73 unselected cases of pernicious anemia in relapse treated with folic acid (parenteral or orally). The number of patients is sufficient for classification according to erythrocyte levels, into 3 statistically significant groups for folic acid and into 5 significant groups for liver extract. The average rate of erythrocyte regeneration for each group is shown in Table I and in Chart I. From a study of the erythrocyte levels attained on the 14th day, it is evident that there is no marked difference between the liver-

treated cases and those receiving folic acid. As can be seen from Table I, and better from Chart I, at 30 days there is considerable difference in favor of the liver-treated groups. If, at 30 days, we compare all 80 liver-treated patients with all 73 treated by folic acid, there is an average difference of 0.6 million erythrocytes in favor of those treated with liver extract. For an individual case such a difference would not be significant, but it is of statistical importance when averages of large groups are involved. Also

TABLE I

Range of Initial Erythrocyte Levels Millions cu./mm.	Number of Patients	Average Erythrocyte Levels Millions cu./mm.			Average daily increment Thousands cu./mm.
Liver Extract					
0.60-0.99 incl.....	8	0.83	2.60	3.57	91
1.00-1.49 incl.....	24	1.23	2.69	3.91	89
1.50-1.99 incl.....	20	1.70	2.94	4.04	78
2.00-2.40 incl.....	8	2.21	3.41	4.40	73
2.50-3.00 incl.....	20	2.73	3.68	4.62	63
Folic Acid					
0.75-0.88* incl.....	4	0.82	2.64	3.24	81
0.99-1.49 incl.....	29	1.20	2.61	3.56	79
1.50-1.99 incl.....	22	1.69	2.50	3.47	59
2.00-3.00 incl.....	22	2.42	3.18	3.64	42

\* Data not used in analysis—number of patients too small.



from data presented in Table I it has been possible to calculate the average daily rate of erythrocyte regeneration for each group of patients—these figures also demonstrate that liver extract has produced better results.

During the first years of liver therapy great emphasis was placed upon the character and extent of the reticulocytosis produced by peroral liver therapy. An early sharp rise in the percentage of reticulocytes in the peripheral blood was interpreted as an indication that the extract used was very potent and that a maximum amount of active material had been given. Cohn, Minot, Alles and Salter<sup>2</sup> were the first to formulate relationships between the reticulocytes and erythrocytes in the peripheral blood. In 1930 Riddle<sup>7</sup>, using data obtained from 68 patients receiving oral liver therapy, proposed a formula for the expected reticulocyte response at any given level of erythrocytes. In 1933 Bethell and Goldhamer<sup>1</sup> proposed a slightly different formula based on data obtained from the administration of stomach perorally and liver extract given intravenously. In 1938 Isaacs and Friedman<sup>3</sup> proposed a formula based on data obtained from the intramuscular administration of liver extract. Subsequently, the character and extent of the reticulocyte response became the "yardstick" for evaluating the potency of the various preparations of liver or stomach used in the treatment of pernicious anemia. Extensive clinical experience with the intramuscular injection of liver extract has demonstrated several shortcomings in this method of determining potency: (1) extreme variations in the reticulocyte "peaks" produced by the same lot of liver extract in patients having essentially the same initial erythrocyte level; (2) the appearance of a marked

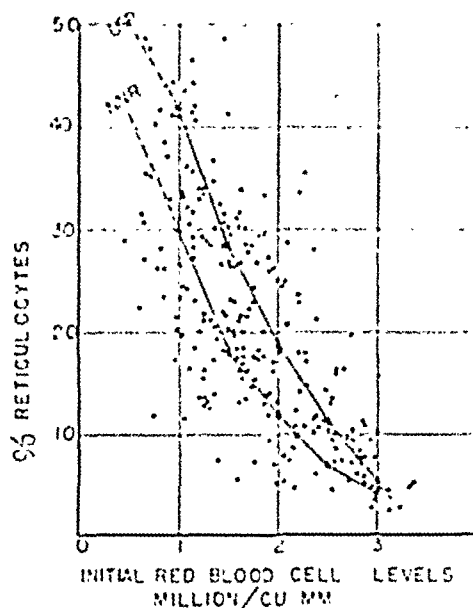
reticulocyte "peak" without subsequent and adequate regeneration of erythrocytes; (3) almost complete absence of reticulocytosis, followed by the regeneration of erythrocytes at a maximum rate. As early as 1933 Murphy<sup>4</sup> pointed out the lack of uniformity encountered in the reticulocyte "peaks" and noted that the rate of erythrocyte regeneration was much more constant and suggested that it might well be a better "yardstick" for estimating potency of anti-anemia products. Analysis of Murphy's data for 48 patients shows as much as 300% difference between the high and low reticulocyte peaks observed for a given initial erythrocyte level. Chart 2 contains data for the reticulocyte "peaks" of 227 unselected cases of pernicious anemia in relapse treated with liver extract\* given intramuscularly. In order better to evaluate and compare these data, there have been included a curve constructed from data supplied by the U.S. Pharmacopoeia Anti-anemia Preparations Advisory Board<sup>6</sup> and a second curve prepared from data supplied by the Council on Pharmacy and Chemistry<sup>5</sup> in 1936.

In the group of patients treated with liver extract (Chart 2) with erythrocyte levels between 0.50 and 0.99 million/cu. mm., the lowest reticulocyte "peak" was 11.8%, the highest was 48.8%. Between 1.00 and 1.49 levels the lowest observed "peak" was 7.5%, the highest was 48.8%. For levels between 1.50-1.99 the lowest "peak" was 5.3%, the highest was 34%. In the last group, with levels between 2.00-2.50, the lowest "peak" was 4.7%, the highest 28.8%. A study of the data presented in Chart 2 indicates that the figures set forth by the U.S.P. Anti-anemia Preparations Advisory Board for expected reticulocyte "peak" at various erythrocyte levels are too

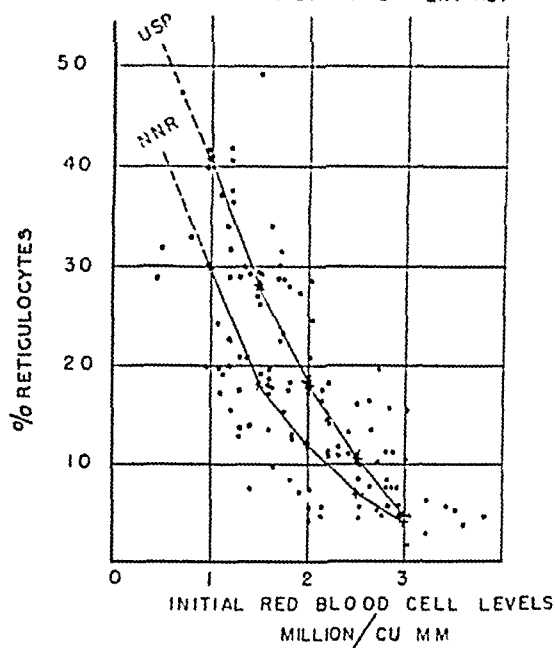
\* The data on reticulocyte "peaks" have been obtained from the clinical assays of liver extract prepared by Lederle Laboratories, Inc.

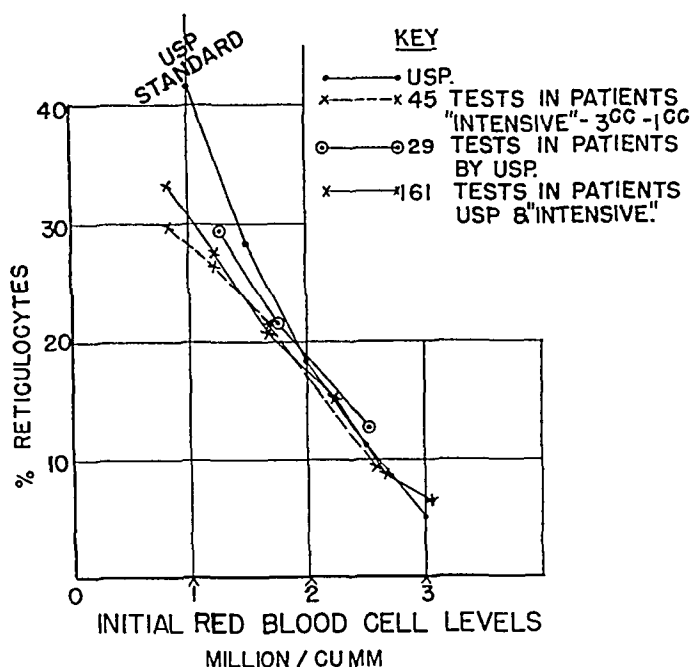


RETICULOCTE  
RESPONSES OBSERVED IN 278  
PATIENTS WITH PARENTERAL  
LIVER THERAPY

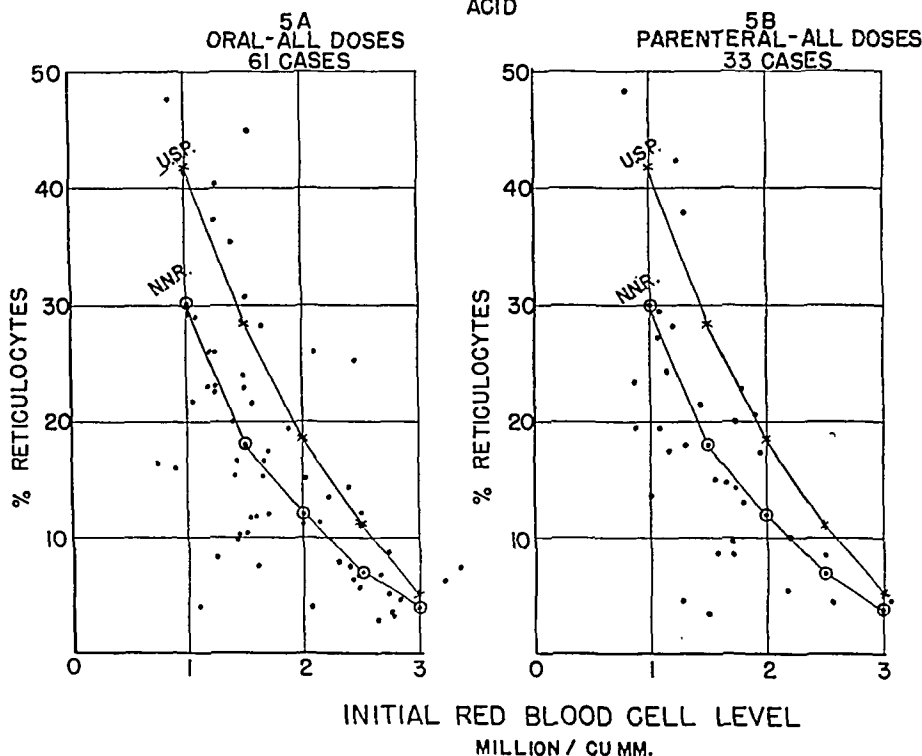


RETICULOCTE  
RESPONSES OBSERVED IN 113 CASES  
FROM ONE CLINIC & ONE BRAND OF EXTRACT





RETICULOCYTE RESPONSES IN PERNICIOUS ANEMIA (IN RELAPSE) TREATED WITH FOLIC ACID

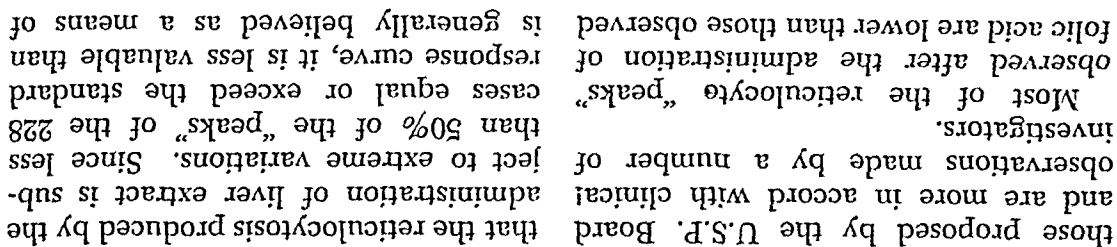


high, particularly for the lower erythrocyte levels (0.5 to 0.99; 1.00 to 1.49; 1.50 to 2.00 millions/cu. mm.). To eliminate, as far as possible, any effects due to different methods of staining and to the counting by different investigators, we have presented the data

on reticulocyte "peaks" of 113 patients from one clinic (Chart 3) with all erythrocyte and reticulocyte counts made by one person, and all patients receiving the same brand of liver extract. These data also demonstrate that the U.S.P. "standards" are too

high as only 46 out of the 113 responses meet the prescribed U.S.P. requirements. Chart 4 shows the U.S.P. standard curve; data for 29 tests made by the U.S.P. method; 45 tests based on intensive liver therapy (pre-U.S.P.) and a curve based on a collection of 161 assays of liver extract. The composite curve based on 161 assays suggests that it might be desirable to modify the "standards" set forth by the U.S.P. Anti-anemia Preparations Advisory Board, somewhat as follows:

**Discussion.** From the data presented in Charts 2, 3, 4, 6, it is evident



evaluating the potency of anti-anemia preparations.

**Summary.** A comparison of the hematopoietic response caused by liver extract or folic acid over a 30-day period, in patients with Addisonian pernicious anemia in relapse, indicates that the rate of erythrocyte regeneration is higher with liver extract than with folic acid.

The variations in the reticulocyte peak observed at any given erythrocyte level are too great to permit use of this physiological reaction as a quantitative measure of the potency of anti-anemia preparations. Certain revisions (for the lower erythrocyte levels) for U.S.P. "standards" are suggested.

Usually the reticulocyte "peak" is much lower with folic acid than has been found for liver extract.

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# SEVERE PAROXYSMAL CARDIAC PAIN AS A PRODROME IN IDIOPATHIC EPILEPSY

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An "aura" is generally considered to precede the convulsion in epilepsy by 1 to 5 minutes, rarely more. Usually the aura instantly announces the coming fit. Prodromata, on the other hand, are symptoms which may occur hours or days before the actual fit. Yet distinction may not prove a simple matter, for some of the prodromal symptoms may continue virtually to the moment of onset while others are placed by different observers in different categories.<sup>8</sup>

In general, prodromata fall into one of 4 groups: (1) motor, (2) sensory, (3) psychical and (4) visceral.

The most common of all are the motor type, and of these, myoclonic twitches or sudden starts affecting one or more limbs occur most frequently. This motor jactitation occurs during the early morning hours or when rising out of bed.

The sensory phenomena are manifested by headache, vertigo, recurrent flashes of light or tinnitus aurium.

The psychical type demonstrate alteration in mood, irritability, depression, a desire to be left alone, or anxiety.

The visceral prodromata may manifest themselves by anorexia or the reverse (ravenous appetite), dyspepsia, flatulence, cutaneous eruptions (erythema, pruritus), malaise, a sense of oppression or tightness across the anterior aspect of the chest. The visceral group comprises symptoms of circulatory, respiratory, vasomotor, vesical, rectal and pupillary nature. It is

apparent, therefore, that disturbance in function occurs in organs innervated by the vagus nerve and presumably starts in vagal nuclei on the floor of the fourth ventricle and adjacent to the vasomotor centers.

Obscurities arise when one approaches the question of epileptic seizures of visceromotor or viscerosensory origin. On general grounds, participation of these centers in epileptiform manifestations must be conceded. The sudden pallor of many cases with petit mal and the "nervous faints" are instances in point. Earlier writers<sup>3</sup> termed these episodes "vagal or vaso-vagal attacks" and because of their periodicity they were thought to be of the nature of epileptiform discharges in these lower centers.

Severe paroxysmal pain of the characteristic cardiac type was observed as a prodromal manifestation of epilepsy in 2 young women, one of whom had rheumatic heart disease, which made the etiology of the cardiac pain more perplexing.

**Case Reports, CASE 1.** V. J., a 34-year old colored female, stated that on Nov. 25, 1947, at 1 p. m. while leaving a cafeteria in the building where she was employed and climbing up one flight of stairs she experienced a constricting pain over the precordium which radiated to the left arm and scapula. This was followed by shortness of breath and unconsciousness. She was then brought to the company doctor where she regained consciousness, but was still orthopneic and dyspneic. She was given amyl nitrite inhalations and morphine sulfate

hypodermically, but showed no improvement, and so transfer to the hospital was advised. The dyspnea persisted in the admitting room of the hospital, and she was sent to a medical ward with a tentative diagnosis of acute coronary insufficiency.

**Previous History.** The patient stated that she had been more or less sickly all her life and was troubled with headaches which were made worse during menstrual periods. There was no history of epilepsy or migraine in the family and she had given birth to 3 children, the last a Mongolian idiot. There was no history of rheumatic fever or syphilis. In February, 1944, a hysterectomy was done and one year later patient began to have typical "grand mal" epileptic seizures. The aura, at first, consisted of a "queer feeling" throughout the body. At first she had about 3 seizures a month. From March until June, 1945, she was at a health resort in Arizona, but continued to have the same number of convulsions. On one occasion she attempted suicide because of inability to hold a job on account of her illness. At the time of her admission to the hospital she had been taking dilantin 1.5 gr. t.i.d. and phenobarbital gr. 1.5 as prescribed by a dispensary that she had been attending. Despite medication she continued to have convulsions at irregular intervals. This was the first time the convulsion was preceded by pain over the heart.

**Course and Progress.** The patient was very intelligent and cooperative. She was anxious to do anything that would make her well. While at the hospital she was observed during several typical attacks. She would suddenly have severe precordial distress which was described as a "pressing" feeling which radiated to the left arm and scapula. This would be followed by dyspnea and orthopnea. She was given various cardiac drugs such as nitroglycerin, amyl nitrite and aminophylline intravenously with no apparent effect. After a period of from 15 to 30 minutes she would go into a typical grand mal convulsion. Status epilepticus occurred on one occasion while in the hospital which was controlled by sodium amytal intravenously.

Examination disclosed a thin, apprehensive, colored female. The pupils reacted to light and soon accommodation, fundi were normal. She had normal fields of vision and active corneal reflexes. Motor power was good. The superficial reflexes were normal and the deep reflexes were hyperactive. Light touch, position and stereognosis were normal. Gait showed good coordination. The heart and lungs were normal. Spinal fluid examination revealed the following: pressure 80mm., clear and colorless, normal dynamics, cell count 4, Pandy and colloidal gold negative, Wassermann negative. Blood count and blood Wassermann were negative. The chest X-ray and electrocardiogram were normal. X-rays of skull in anteroposterior and lateral views were normal. Electroencephalogram revealed low voltage, 11 to 12 per second activity. Parietal and frontal areas showed bursts of 6 to 8-per second and bursts of 4 to 6-per second waves, moderate build-up with hyperventilation. Impression: moderately abnormal electroencephalogram with frequent slow waves most marked in frontal and parietal areas.

**Case 2.** S. D., a 34-year old white female, married, one child, stated that on Christmas night, 1946, while reading a magazine, she was suddenly seized with a severe agonizing pain over the lower sternal and precordial areas which radiated down the left arm as far as the wrist. She stated the pain was unbearable and begged for relief. Her face was pale and covered with clammy perspiration. She was sitting up in bed with her head thrown backward as if this were the only position that would afford some degree of relief. Tachypnea was present, but seemed to be a result of the severe pain. The temperature and pulse and blood pressure were normal. She was given morphine sulfate and atropine hypodermically and after 15 minutes, the condition remained unchanged. She was then taken to the hospital, given oxygen and the attack gradually subsided.

**Previous History.** Patient was an adopted child and had no information about her parents. She was always highly emotional and given to fainting spells. There was no history of rheumatic fever



Fig. 1.—Case 2. Chest X-ray showing enlargement of the left ventricle and a fullness in the region of the pulmonary conus; Heavy hilar shadows and thickened interlobar fissure.

in childhood. At the age of 17 she eloped and was happily married. At the time of her pregnancy, heart murmurs were discovered and she was advised to take things easy. However, she was weak for 5 months after delivery, but for the next 4 or 5 years was fairly well. There was no history of cardiac failure at any time. Physical Examination. On Dec. 26, the day after admission to the hospital, the patient sat up in bed as if nothing had happened. She was naturally sallow in color. The temperature, pulse and blood pressure were normal. No rales were heard. On percussion the heart was enlarged to the left and an increased area of dullness was noted in the 3rd left inter-space adjacent to the sternum. At the apex a distinct presystolic thrill was palpable. On auscultation over this area, a low pitched, rumbling murmur beginning in mid-diastole with presystolic accentuation and a short systolic murmur were audible. An early soft diastolic murmur was heard. The blood findings were as follows: Hemoglobin 11.5 gm., red blood cells, 3,800,000, white cells, 13,100, with 70% neutrophils, 26% lymphocytes and 4% monocytes. Course and Description of Typical Attack. About 3 days after admission to the hospital the patient was suddenly awakened in the early morning hours by an agonizing, excruciating precordial pain ray was negative. Examination of the urine was negative. The Kahn and Wassermann tests were negative. The blood findings were as follows: Hemoglobin 11.5 gm., red blood cells, 3,800,000, white cells, 13,100, with 70% neutrophils, 26% lymphocytes and 4% monocytes. Course and Description of Typical Attack. About 3 days after admission to the hospital the patient was suddenly awakened in the early morning hours by an agonizing, excruciating precordial pain

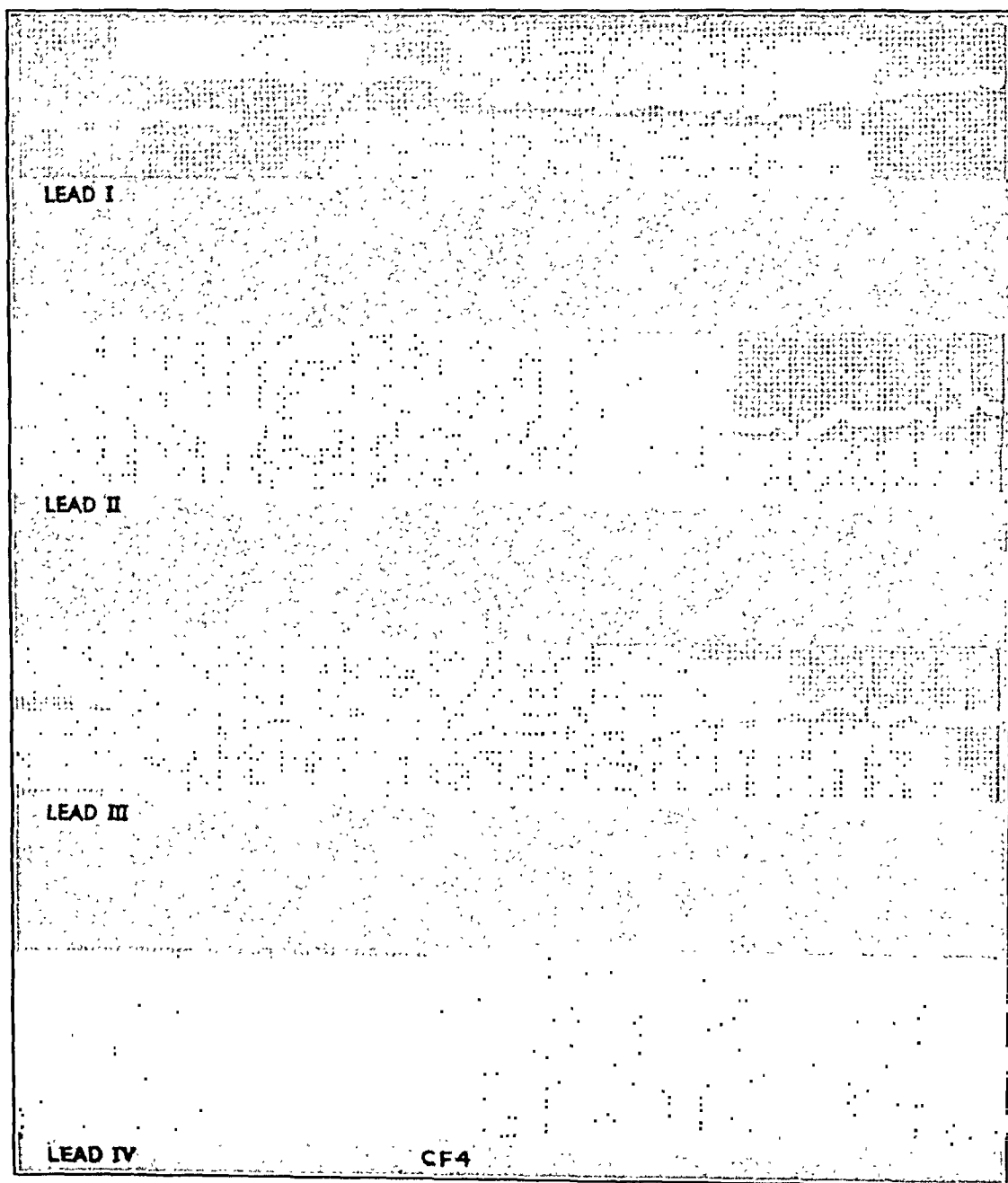


Fig. 2.—Case 2. Electrocardiogram taken during the paroxysm of pain, showing slight depression of S-T segment in CF<sub>4</sub>. In addition, there is slight depression of S-T<sub>2</sub>, low to inverted T waves in Lead I, and right axis shift.

which radiated to the left shoulder and left arm. She was sitting up in bed clutching her left breast and at the same time tearing her nightgown into shreds. Her face was pale and slightly cyanotic about the lips and her forehead covered with beads of perspiration. Her head was extended backward in an opisthotonus position. She made attempts to get out of bed as it appeared as though walking would relieve her. She was markedly

dyspneic but no rales were heard. Several of the hospital personnel were about her bed at the time of the pain, but she did not seem cognizant of their presence. Various drugs were tried, such as sublingual administration of nitroglycerine, amyl nitrite, and aminophylline intravenously, but these were of no avail. An electrocardiogram (Fig. 2) taken at this time showed only very slight depression of S-T<sub>4</sub> and this was not thought deep enough to be



diagnostic. After oxygen administration, the attack gradually subsided, although when these agents were withheld in other attacks they subsided in approximately the same length of time. The patient seemed confused and bewildered after the attack and seemed surprised to note the look of concern on the faces of those about her. There then followed an aftermath of somnolence and much weakness so that she was unable to get out of bed for days at a time. She had several of these episodes in the month she remained at the hospital, some being milder than others. There was always hyperesthesia over the apical region of the heart.

It was later learned from the husband that in 1941 he had come home from work one night and found his wife lying on the couch in a "trance" as he called it. A local doctor was called who diagnosed a nervous disorder and ordered the patient to the hospital. The patient remained in the hospital for 10 days and had no attacks of any kind. She was discharged undiagnosed. The urinalysis and blood count were normal. An intracerebral lesion was suspected and skull X-rays were negative. The sella turcica was small but within normal limits. Spinal fluid examination revealed the following: Wassermann negative, sugar 76, protein 38, Lange colloidal gold test 1111100000.

The electrocardiogram at that time showed sinus bradycardia, normal axis and rather prominent T waves in the standard and precordial leads.

It was later learned that at times she would complain of being tired, weak and warm and would lie down. Right after this she would not respond to questions and her husband noted a vacant look or fixed expression with facial pallor and slight twitches of the lips and tongue. On one occasion while tending to her baby she suddenly found herself on the floor with a "goose egg" on the back of her head.

**Discussion.** Pain over the heart may be due not only to pathologic conditions in the heart or aorta, but also to abnormal states of the nervous system, both cerebrospinal and vegetative. Therefore, in an analysis of altered

cardiac sensation the existence of extraneous factors entirely apart from the disease under investigation must be recognized and their relative importance in the production of symptoms must be evaluated.

From a description of these 2 cases it is obvious that the various manifestations they exhibit place them in a different category from that of patients with so-called classical symptoms of angina pectoris. First, the pain was spontaneous and not preceded by effort or emotion. The distress had no relationship to meals and was never preceded by nausea or vomiting. Rest did not offer any relief. It is also of interest in that the attacks occurred over a certain "crucial" period, and then the patient might remain free from pain for months to years.

The first case, however, closely simulated a true anginal syndrome, and in fact, the patient was treated as an acute coronary occlusion in 2 different institutions. While under observation at the hospital, it was noted that each convulsion was preceded by a paroxysm of chest pain of 15 to 60 minutes duration and it was interesting that each resident physician who saw her in the early attack administered nitrites, aminophylline, oxygen and other cardiac drugs. These measures seemed to have no effect on the pain. After each seizure she would fall asleep for several hours and when she awoke the pain had disappeared.

In the second case, the cause of the pain was a little more difficult to analyze. The patient was known to have chronic rheumatic heart disease with mitral stenosis and insufficiency and aortic regurgitation. It is commonly known<sup>5,7</sup> that aortic insufficiency may be associated with typical attacks of angina pectoris. This has been explained as due to the low diastolic pressure which results in incomplete filling of the coronary arteries and thus

produces a relative anoxemia of the heart. Even uncomplicated mitral stenosis<sup>1,2,7</sup> may give rise to an anginal syndrome probably due to inadequate coronary circulation on effort. Pain in rheumatic heart disease may also be due to (1) pericarditis, (2) active rheumatic heart disease with coronary artery lesions<sup>4</sup>, or (3) added effort of paroxysmal tachycardia, paroxysmal flutter or fibrillation, or in congestive heart failure.

Schwartz<sup>6</sup> described a form of severe paroxysmal cardiac pain in 5 young adults all of whom had rheumatic heart disease with aortic insufficiency. His cases were also characterized by violent palpitation of the heart, vasomotor phenomena, marked pulsations of the peripheral vessels and increased blood pressure. These patients showed various psychopathic stigmata and some were given to syncopal attacks. However, he did not consider any relationship of these symptoms to epilepsy.

Gowers<sup>3</sup> states that a cardiac aura is not common in epilepsy. He cites

the case of a boy, aged 16 years, subject to fainting spells, each preceded by stabbing pains over the heart followed by loss of consciousness. On return of consciousness after a minute, he struggled and had to be held down, evidently in the hysteroid state that so often follows minor epilepsy, but never occurs after cardiac syncope. Yet the case had first been regarded as one of simple "cardiac faints" on account of the initial pain, which was really an epileptic aura.

**Summary.** Two cases of idiopathic epilepsy are described in which the prodromata consisted of severe paroxysmal cardiac pain simulating true angina pectoris. In one case, though rheumatic aortic insufficiency and mitral stenosis and insufficiency were present, it was felt that these valvular lesions did not contribute to the angina pectoris syndrome.

It should be emphasized that severe precordial pain may be due not only to intrinsic disease of the heart or aorta, but also to abnormal states of the nervous system.

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# PROGRESS

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## MEDICAL SCIENCE

### MEDICINE

Under the Temporary Charge of

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### DYNAMICS OF THE HYOGLYCEMIC REACTION

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Clinical manifestations attributable to an abnormal lowering of the blood sugar were observed even before the discovery of insulin. In 1921, Joslin<sup>55a</sup> reported several cases of hypoglycemia in extremely undernourished diabetics, one of whom died with a blood sugar of 40 mg. per 100 cc. One year later, Woodratt<sup>121</sup> observed a patient with diabetes who died in hypoglycemic convulsions; he also referred to a fatal case of hypoglycemia noted by Williams in whom no insulin was used. Harrop<sup>56</sup> cited a patient with severe diabetes and extreme emaciation observed by Herman; the blood sugar 5 hours before death was 17 mg. per 100 c.c. The first description of hypoglycemic reactions in animals injected with insulin was given by Banting, Best and their collaborators<sup>7</sup> and was soon followed by reports of Banting et al.<sup>8</sup> on the occurrence of such reactions in diabetics treated with insulin. Shortly thereafter it was realized that the described symptom-complex might develop in non-starved individuals even when no exogenous insulin was taken. Harris<sup>17</sup> was the first to suggest that spontaneous hypoglycemia might be produced by excessive secretion of endogenous insulin and he proposed the term of hyperinsulinism for this disease entity. In 1927, Wilder et al.<sup>120</sup> reported the first case of hyperinsulinism resulting from pancreatic carcinoma. Since it was noted that (a) an overdose of insulin produced a critical depression of the blood sugar accompanied by a group of characteristic clinical symptoms and (b) the spontaneous occurrence of such symptoms was associated with hypoglycemia, the subnormal blood sugar was assumed to be the cause of the symptoms. This explanation soon proved unsatisfactory since on occasions after the administration of insulin, hypoglycemic symptoms were present even though the

blood sugar was not critically lowered. In other instances, symptoms were absent even when the blood sugar was markedly depressed. Again, Banting, Best and their associates<sup>7,8,40</sup> were the first to make such observations. Similar findings were later described by many others in various types of experimental and clinical hypoglycemia<sup>27,31,32,33,48,49,50,52,62,63,65b,66a,67,73,79,86,92,93,99,103,105,111,112,114,116,119a</sup>.

To account for the lack of parallelism between the clinical and laboratory findings in hypoglycemia, it was suggested that in the absence of critically low blood sugar levels, symptoms were produced by a rapid fall of the blood sugar<sup>3,21,79,94,112,119b</sup>. However, the question why some patients remained symptom-free in spite of a marked depression of the blood sugar was left unanswered.

Two explanations were offered to account for the mechanism whereby lowering of the blood sugar produced clinical symptoms. Since some of the symptoms were similar to those which followed the injection of epinephrine (mydriasis, tremor, tachycardia, etc.), some workers<sup>12,34,71,72,112</sup> ascribed the hypoglycemic symptoms to a secondary release of epinephrine. Other investigators implicated the central nervous system. In 1928, Joslin<sup>65c</sup> stated "It may possibly be that through the lowering of blood sugar, certain oxidative processes become depressed to such a degree that the brain cells are affected in much the same manner as in asphyxia." This view found support in the studies of Lennox<sup>77</sup> and of Himwich and Nahum<sup>56</sup> which disclosed that the respiratory quotient of the brain approximated unity, a finding which indicated that the brain derived its energy chiefly from carbohydrate. Thus, a diminished supply of glucose to the brain such as might occur in hypoglycemia would reduce the cerebral metabolism and thus produce the

clinical picture of hypoglycemia. From observations made during insulin shock therapy, Frostig<sup>42</sup> and Himwich<sup>54</sup> divided the symptoms of acute hypoglycemia into 5 phases and correlated the sequence of these phases with the depression of the metabolic rate at various levels of the brain.

More recently, it was found that the effect of hypoglycemia on the function of the brain was an indirect one. Holmes<sup>59</sup>, Dameshek et al.<sup>28</sup> and particularly Himwich and Fazekas<sup>55</sup> showed that low blood sugar values diminished cerebral oxidative metabolism, whereas the administration of glucose was followed by an increase in the oxygen uptake by the brain. Cerebral anoxia as the immediate factor in the production of hypoglycemic symptoms was further accentuated by other studies of Himwich and by those of Gellhorn and Kessler<sup>43</sup>.

Feldberg<sup>35,36</sup> noted that the synthesis of acetylcholine by brain tissue was stimulated by low concentrations of glucose and inhibited when the sugar content of the medium was as high or higher than that in normal blood. Since acetylcholine was a convulsant, he suggested that the increased production and release of acetylcholine by the nervous system during hypoglycemia might account for part of the picture of the hypoglycemic reaction.

From the foregoing, it appears that much emphasis has been placed on the variations in blood sugar during hypoglycemic reactions and not enough on the dynamics of cerebral sugar metabolism. It is obvious, however, that the utilization of sugar by the brain cannot be measured by the rate of supply of glucose but rather by the magnitude of cerebral consumption of this fuel in relation to the energetic needs of the brain. While it is readily understood that a low blood sugar may lead to carbohydrate starvation of the central nervous system accom-

panied by clinical symptoms of hypoglycemia, the absence of the hypoglycemic reaction even when the blood sugar is critically depressed can be explained only by assuming that (a) the decrease in blood sugar is not necessarily equivalent to a decrease in brain sugar and (b) a low blood sugar does not greatly affect a brain whose energy requirements are relatively low.

Evidence is available to support the view that the cerebral consumption of sugar does not parallel blood sugar variations. Kerr and Best<sup>68</sup> postulated that as a result of utilization of sugar by the central nervous system, the sugar content of the brain is always lower than the blood sugar level. On the other hand, Himwich and Fazekas<sup>55</sup> in experiments with dogs injected with insulin found a glucose uptake of 13.1 mg. per 100 cc. when the blood sugar ranged from 110 to 62 mg. per 100 cc. and only a slight reduction in uptake to 12.5 mg. per 100 cc. when the blood sugar was depressed to between 46 and 25 mg. per 100 cc. As for variations in cerebral energy requirements, Cannon et al.<sup>19</sup> observed that in cats deep chloralose anesthesia reduced or abolished the insulin reaction although it did not prevent the fall of the blood sugar. Höglér<sup>57</sup> demonstrated that during veronal or luminal anesthesia in rabbits even a profound hypoglycemia was not accompanied by convulsions. Of particular significance were the observations of Harrison<sup>49</sup> who in diabetic children under 12 years of age found insulin reactions to occur at a lower blood sugar level than in adults. Similarly, White<sup>115</sup> noted the infrequent occurrence of hypoglycemic reactions in babies with subnormal blood sugars. Himwich<sup>54</sup> in commenting on White's paper suggested that since the metabolic rate of a newborn infant was much lower than in the adult, the energy expenditure of the brain of the

infant must of necessity also be much lower than in the adult.

On the other hand, it is conceivable that with normal blood sugar values the rate of supply of sugar to the brain may be decreased beneath the cerebral metabolic requirement. Although there is no evidence available to support such a view, this hypothesis is suggested by analogy on the basis of studies on the distribution of fructose between arterial blood and brain tissue. Klein et al.<sup>70</sup> in experiments with eviscerated rats recently demonstrated that the proportion of intravenously administered fructose which passes to the brain is so small that this sugar cannot maintain normal brain function. By assuming that passage of glucose to the brain may under certain circumstances be similarly disturbed, one might explain the occurrence of hypoglycemic manifestations in absence of laboratory evidence of hypoglycemia.

Another dynamic factor that must be considered is the ability of the brain not only to absorb but also to release sugar. Himwich and Fazekas<sup>55</sup> reported that when the blood sugar was raised to high levels by the intravenous administration of glucose, the cerebral sugar uptake was almost doubled (23.5 mg. per 100 cc.). When the blood sugar was rapidly raised and then quickly reduced by administration of both glucose and insulin, the brain secreted glucose into the blood stream during the fall of the blood sugar, with the result that more sugar was found in venous than in arterial blood. These data are in keeping with the earlier observations of Rosenow<sup>102</sup> who in a case of spontaneous hypoglycemia found no arterio-venous difference in blood sugar and with those of Holzer and Klein<sup>60</sup> and Butt and Keys<sup>18</sup> who in hypoglycemia after insulin found the oxygen saturation of venous blood to be of the same magnitude or even higher than that of

arterial blood. It is to be noted, however, that these writers ascribed such arterialization of the venous blood to an increased blood flow whereby less oxygen would be given off by the blood to the tissues rather than to the activity of the tissues themselves.

Mention should also be made of the equilibrium which exists between the sugar concentration in the blood and in the cerebral fluids. Under normal conditions, the sugar content of the blood is higher than that of the cerebrospinal fluid, the ratio being roughly 2:1. In insulin hypoglycemia, the sugar concentration in the cerebrospinal fluid usually remains unchanged or it may be increased so that the ratio becomes reversed<sup>117</sup>. During hypoglycemic reactions, Gravano<sup>46</sup> found the concentration of glucose in blood and cerebrospinal fluid to be 40 and 163 mg. per 100 cc., respectively, and Sigwald<sup>105</sup> 65 and 100 mg. per 100 c.c.

Constriction of the cerebral arterioles and capillaries may occur in severe hypoglycemia. In irreversible insulin coma, Ferraro and Jervis<sup>39</sup> found endothelial proliferation and obliteration of small vessels and capillaries in the cerebral cortex. These vascular alterations were considered to be a factor in the production of brain anoxia. Reitman<sup>90</sup> reported on the efficacy of vasodilator drugs such as nicotinic acid and amyl nitrite in abolishing hypoglycemic convulsions. More recently, Sindell<sup>106</sup> published his findings on 3 patients with hypoglycemic coma who recovered following the use of amyl nitrite by inhalation. However, cerebral vasoconstriction does not seem to play a significant part in the causation of milder hypoglycemic reactions since according to Cobb and Lennox<sup>20</sup> the cerebral circulation is not impaired during hypoglycemia as long as there is no loss of consciousness. These writers also ascribe the electroencephalographic changes accompanying sub-

normal blood sugars not to circulatory abnormalities but to changes in blood chemistry.

From the foregoing, it is evident that carbohydrate metabolism of the brain is subject to a number of factors. The variations of glucose in the blood are undoubtedly important but of major significance appears to be the active participation of the brain in controlling its own consumption of glucose. This may represent a mechanism whereby the brain tissue can protect itself against a dearth of this nutritive substrate. This dynamic concept of cerebral carbohydrate metabolism may provide a better understanding of the hypoglycemic reaction. It may explain the reported inconsistencies between clinical and laboratory findings in hypoglycemia since it may account for both the absence of symptoms with distinctly hypoglycemic levels as well as for the occurrence of symptoms without subnormal blood sugar levels. In accordance with this concept, the hypoglycemic symptoms may develop (a) when the decrease in blood sugar is very profound and cannot be compensated for by an increased cerebral glucose consumption, (b) when the transfer of glucose from the blood to the brain is appreciably reduced and (c) when the brain tissue is unable to absorb adequate amounts of sugar or to utilize it properly even though the sugar may be supplied at a normal rate. In all these instances, glucose consumption by the brain is diminished below the cerebral metabolic needs. Such cerebral glycopenia may then produce the hypoglycemic reaction either by way of cerebral anoxia, by disturbances in the metabolism of acetylcholine or possibly by still another unknown mechanism.

**Pseudohypoglycemic Reactions.** Symptoms usually associated with hypoglycemia may occur in various conditions in which the carbohydrate

metabolism is not primarily involved, such as epilepsy and hypoparathyroidism.<sup>32</sup> It is significant that in these conditions disturbances of brain function are present as revealed by abnormalities of the electroencephalogram. With regard to epilepsy, the basic nature of this disease is now characterized as cerebral dysrhythmia and further elaboration here appears unnecessary. In hypoparathyroidism, emphasis is usually laid on the depression of serum calcium since this element is known to be essential for the normal function of nerve tissue and for the maintenance of normal neuromuscular excitability. Interestingly enough, the presence of cerebral dysfunction was recently reported in tetany. Albright et al.<sup>1</sup> observed a case of idiopathic hypoparathyroidism in which the electroencephalographic tracing was consistent with the diagnosis of epilepsy. The patient was treated unsuccessfully for epilepsy for many years. Her seizures became less frequent and less severe following antitetanitic treatment with dihydrochloride (hytakerol, A.T. 10). Odoriz et al.<sup>30</sup> described the electroencephalographic abnormalities in hypoparathyroidism as consisting of a diminution in alpha activity and appearance of single spikes as well as trains of 2 to 3 per second waves. Taubenhaus and Engle<sup>10</sup> reported a case of hypoparathyroidism associated with grand mal epilepsy. Correction of the hypocalcemia not only eliminated the tetanic and epileptic symptoms but also diminished the electroencephalographic abnormalities.

The association of hypoglycemia with hypocalcemia and electrocerebral dysfunction was recently reported by one of us.<sup>32</sup> Therapy aimed at only one of the coexisting conditions was followed by partial improvement whereas complete freedom from symptoms was obtained when the treatment was

directed at all the associated conditions. It was not possible to ascertain whether some of the reactions were produced solely by the cerebral dysfunction although such a possibility was suggested. The study was then extended to labile diabetes.<sup>33</sup> In a group of such patients who also exhibited alterations of the electroencephalogram, it was observed that the hypoglycemic incidents so frequent in labile diabetes were only in part caused by subnormal blood sugar levels. Not infrequently the blood sugar was exceedingly high during apparent hypoglycemic reactions. Such reactions could not be overcome by the administration of sugar but could be prevented by the use of anticonvulsive drugs. It was therefore concluded that electrocerebral dysfunction *per se* may produce symptoms identical with those of hypoglycemia and the term "pseudo-hypoglycemic reactions" was proposed for this type of reaction.

Much has been written on hypoglycemia as a factor in the production of epileptic seizures. A critical perusal of the literature discloses that even an extreme lowering of the blood sugar cannot produce either epileptic seizures<sup>9,16,95</sup> or an epileptic type of brain activity although it may enhance the abnormal brain wave pattern in patients with petit mal.<sup>29,30,44</sup>

As for the status of carbohydrate metabolism in parathyroid disorders, the data are contradictory. According to some workers<sup>50,113,118</sup>, parathyropival tetany was accompanied by insulin sensitivity and hypoglycemia both of which were corrected by the administration of calcium. Other observers found that parathyroid extract improved carbohydrate tolerance in patients with diabetes<sup>38</sup> and produced a transient fall of the blood sugar in dogs.<sup>55</sup> Labbe et al.<sup>71</sup> found that calcium salts exerted a hypoglycemic effect in normal and diabetic subjects where-

as Underhill<sup>113</sup> reported that in rabbits administration of calcium accelerated the hyperglycemia and enhanced the glycosuria produced by adrenaline. According to Oliva<sup>91</sup>, glucose caused a slight increase and insulin a slight decrease in serum calcium in normal and diabetic subjects. However, clinical observations indicated the usefulness of calcium in suppression of hypoglycemic convulsions after insulin even though this therapy did not influence the hypoglycemia itself<sup>45,62,63,83</sup>. The beneficial results obtained with calcium salts in hypoglycemia associated with hypocalcemia reported by Fabrykant<sup>32</sup> may of course be explained by the coexistence of these two conditions.

While no attempt is made to connect causally the 3 conditions, hypoglycemia, hypocalcemia and cerebral dysfunction, recent data on the relation between the metabolism of calcium, carbohydrate and acetylcholine indicate that the mechanism involved in the production of clinical reactions in these conditions may be similar.

**Reaction Threshold.** Since there is no absolute relationship between the blood sugar values and hypoglycemic reactions, Sevringhaus<sup>103</sup> suggested that the level at which reactions occur is an individual pattern. John<sup>62</sup> reported that the level may vary even in the same individual from one day to another.

The frequent occurrence of reactions at comparatively high blood sugar values raises the question of a reaction threshold. Fletcher and Campbell<sup>10</sup> stated that "when a reaction has already been experienced, the onset of a subsequent one is usually recognized by the patient when the blood sugar percentage falls to some point between 0.08 and 0.07 per cent." Joslin<sup>65d</sup> observed what he termed "false hypoglycemic reactions" to occur with blood sugar values of from 220 to 290 mg. per 100 cc. In two instances, these

false reactions resembled so closely a true reaction "as to mislead a nurse and an assistant of great experience." From a study of 1000 cases of diabetes, John<sup>63</sup> concluded that in nearly 50% of insulin reactions, the blood sugar was high. On several occasions, he found values between 110 and 394 mg. per 100 cc. Harrop<sup>50</sup> reported blood sugar values between 110 and 150 mg. per 100 cc. in 4 diabetic patients with insulin reactions. It may be assumed that in such cases a certain individual susceptibility to reactions exists since it is common knowledge that the majority of diabetics do not react in this way to insulin.

An unusual sensitivity to insulin may develop as a result of inanition. This was observed in diabetics treated with starvation diets and was ascribed to glycogen deficiency. In a case reported by Joslin<sup>65e</sup>, for instance, a reaction followed the administration of one unit of insulin and in a patient treated by Rosendahl<sup>101</sup> a severe reaction ensued after the administration of 2 units daily for 4 days.

In patients with hypoglycemia accompanied by hypocalcemia and electrocerebral dysfunction, Fabrykant and Pacella<sup>32</sup> noted the frequent occurrence of hypoglycemic symptoms in the absence of critically low blood sugar levels. Since such reactions were prevented by anticonvulsive drugs and calcium therapy, they concluded that because of cerebral dysfunction and hypocalcemia, these individuals were more susceptible to even small variations of blood sugar. In other words, it was assumed that these patients had a lowered reaction threshold; they postulated that anticonvulsive drugs and calcium therapy might have raised the threshold. In a group of labile diabetics with electrocerebral dysfunction<sup>33</sup> a number of reactions occurred with normal or slightly elevated blood sugar levels. Following anticonvulsive ther-



apy, the frequency and severity of such reactions were reduced even though in some instances the insulin dosage was increased. Moreover, following such therapy, the onset of reactions was less abrupt and the reactions yielded easily to small amounts of carbohydrate. It was evident that in these patients as well, the cerebral dysfunction might have decreased the reaction threshold.

In a group of patients with labile diabetes observed by one of us<sup>16</sup>, bellergal proved effective in stabilizing the diabetic state. Since this preparation contains belladonna, ergotamine and phenobarbital, its effect might be explained by the action of its components on cerebral dysfunction. No definite statement can be made with regard to this group of patients since no electroencephalographic studies were made. Interestingly enough, in an unstable diabetic treated by Root<sup>66b</sup>, phenobarbital decreased the sudden onset of hypoglycemic episodes.

From the foregoing, it appears that a reduced reaction threshold may be found in (a) subjects who exhibit frequent insulin reactions; these individuals behave as if they were conditioned by the frequency of reactions and are able to perceive even minor fluctuations of the blood sugar, (b) the hypoglycemia of starvation, in which condition the subjects seem to be so sensitized by the continuous dearth of glucose that minute amounts of insulin result in severe symptoms or even in fatal outcome, and (c) those subjects who in addition to spontaneous or insulin-induced hypoglycemia suffer from other conditions apt to produce symptoms resembling the hypoglycemic complex, such as hypocalcemia and electrocerebral dysfunction.

**Irreversible Reactions From Hypoglycemia.** Under this heading are reviewed briefly those reactions in which

the basic disturbance is no longer functional but structural, i.e., reactions which result from hypoglycemic damage to the brain. A severe and prolonged state of hypoglycemia may produce anatomic lesions in the central nervous system such as edema of the brain, cerebral and meningeal hemorrhages, necrosis of the cortex characterized by degeneration and disintegration of ganglion cells, and swelling of the glia and axis cylinders<sup>6,39,64,66c,75,119c</sup>. It is obvious that such lesions may cause profound alterations in brain function accompanied by various clinical manifestations. Such clinical reactions, however, need not be correlated with the glucose concentration in the blood since they are not in the nature of hypoglycemic but rather post-hypoglycemic phenomena related to brain changes which persist even after hypoglycemia and cerebral glycopenia have been corrected.

The injury to the brain from hypoglycemia may be of short duration and reversible<sup>95</sup> or it may be irreversible. Thus, the hypoglycemic state and unconsciousness may persist for days and be followed by slow recovery or there may be residual and permanent abnormalities such as epilepsy, mental deterioration and idiocy<sup>2,4,64,69,119d</sup>. In some instances, the patients fail to survive the attack, and death may occur 3 to 23 days after the insulin has been discontinued and the blood sugar elevated to normal or hyperglycemic values<sup>64,75,100</sup>. Such fatal episodes may develop in hyperinsulinism as well as in hypoglycemia produced with both the unmodified and the slow acting insulins. In 1922 Woodyatt<sup>121</sup> reported the case of a patient with diabetes and inanition. The urine was sugar-free on admission. The diet was increased and a calculated dose of insulin was given. Hypoglycemic shock resulted during which the blood sugar was found to be too low to be determined.

The administration of sugar was followed by a rise of the blood sugar to hyperglycemic values with the production of glycosuria but the patient died without regaining consciousness.

In hypoglycemia produced by an overdose of protamine-zinc insulin, symptoms may be absent for hours and fatal convulsions from brain damage may develop after the blood sugar has been raised to normal or even hyperglycemic levels. Bollman<sup>11</sup> made dogs hypoglycemic for 50 to 60 hours with protamine-zinc insulin. When sugar was administered to restore the blood sugar, the animals went into fatal convulsions and autopsy revealed a large number of petechial hemorrhages in the brain. Sherrill and MacKay<sup>104</sup> also produced a stuporous hypoglycemia in dogs with protamine-zinc insulin associated with a fall of the blood sugar to between 20 and 30 mg. per 100 cc. for 24 to 48 hours. Here again, elevating the blood sugar to normal by the administration of sugar failed to protect the animals from death.

Reactions which develop as a result of brain damage from severe hypoglycemia may of course show great similarity to reactions in which there is no brain damage. While these reactions are initiated by critically low blood sugar values, they cannot be regarded as true hypoglycemic episodes, since they are produced by structural and not functional changes in the brain. The term "post-hypoglycemic encephalopathy" suggested by Jones<sup>61</sup> seems more appropriate to designate this type of reaction.

**Role of Epinephrine in Insulin Reactions.** As mentioned earlier, in 1923 Boothby and Wilder<sup>12</sup>, suggested that insulin reactions were due to a secondary release of epinephrine since the symptoms noted during hypoglycemia were not dissimilar to those observed after the administration of epinephrine.

Soon thereafter, Riddle et al.<sup>97</sup> lent support to this concept by demonstrating that repeated injections of insulin caused hypertrophy of the adrenal glands. Further evidence strengthening this concept was provided by the work of Cannon<sup>19</sup>, Houssay<sup>61</sup> and Macleod<sup>78</sup> on the role of the sympathetic-adrenal system in the mobilization of endogenous glucose in response to subnormal blood sugar values.

In 1901, Blum<sup>10</sup> demonstrated that epinephrine raised the blood sugar by mobilizing liver glycogen. This observation has been confirmed repeatedly. Later, the Coris and other workers<sup>22,23,24,25</sup> showed that epinephrine hyperglycemia resulted rather from decreased utilization of the blood sugar in peripheral tissues. The observation that insulin accelerated utilization of blood sugar and inhibited hepatic glycogenolysis produced by epinephrine established the antagonism between these two hormones<sup>24,25</sup>.

Much experimental work accrued to fortify this concept of insulin-epinephrine antagonism. Britton et al.<sup>15</sup> showed that animals deprived of their adrenal function were hypersusceptible to the hypoglycemic effect of insulin. Crandall and Cherry<sup>26</sup> observed that adrenalectomized or adrenal denervated dogs went into shock as soon as one hour after the injection of 15 units of insulin and they postulated that the secretion of epinephrine is stimulated when the blood sugar level drops to a point between 50 and 60 mg. per 100 cc. Brandt and Katz<sup>13</sup> demonstrated the presence of vasoconstrictor substances, presumably epinephrine, in human blood during reactions induced by the intravenous administration of 20 to 30 units of insulin. In this regard, it is interesting to note that in patients undergoing insulin shock therapy, Heilbrunn and Liebert<sup>53</sup> found little or no vasoconstrictor substances in the blood of those readily

mediated by the central nervous system and the adrenal medulla. In the present paper, the importance of the central nervous system in the production of the clinical hypoglycemic state has been stressed. The homeostatic regulation of the blood sugar during emergency situations may represent an attempt of the adrenal medulla to correct the subnormal blood sugar concentration. Whether this process will be effective in abolishing the clinical symptomatology will depend primarily on the degree to which cerebral function has been depressed and on the ability of the brain to respond to the increase in blood sugar.

**Role of Potassium Deficiency in the Hypoglycemic Reaction.** In reactions from an overdose of insulin, some of the hypoglycemic manifestations may be related to potassium depletion. A decrease in serum potassium after the administration of insulin was reported soon after the discovery of insulin by Harrop and Benedict<sup>17</sup> and by Briggs et al.<sup>18</sup> In a case of spontaneous hypoglycemia, McQuarrie et al.<sup>19</sup> observed a rise in blood sugar with partial relief of symptoms following administration of potassium chloride. They felt that the use of potassium salts may be helpful in the prevention of insulin reactions in diabetes. However, the clinical significance of hypopotassemia in diabetes remained unrecognized until the recent report of Holler<sup>20</sup>. From Holler's observations and those which followed his paper<sup>17,18,20,21</sup>, the syndrome of potassium deficiency after insulin may be pictured as consisting of muscular weakness, extreme respiratory distress, increased pulse pressure, heart dilation, cardiac arrhythmia, rise in venous pressure and a group of characteristic changes in the electrocardiogram. In the past, some of these symptoms were ascribed to the depression of the blood sugar but recent evidence

are also certain emergency mechanisms going into insulin shock. In those in whom insulin produced mild symptoms such as drowsiness and perspiration, there was a sharp rise in vasoconstrictor elements in the blood which they presumed to be epinephrine. In an indirect fashion, Kugelmann<sup>22</sup> attempted to show an increased production of epinephrine during insulin hypoglycemia; he injected ergotamine with insulin into 10 patients and obtained hypoglycemia without the circulatory signs in 4 of these. These patients, however, exhibited tiredness, weakness and hunger. Even if one assumes the validity of such observations, it is obvious that no correlation has been shown to exist between epinephrine secretion and hypoglycemic reactions. The homeostatic regulation of the blood sugar is undoubtedly under the control of the endocrine system. However, the part played by the adrenal medulla is probably insignificant. The experiments quoted above indicating the increased sensitivity of the adrenalectomized animal to insulin must take into account the fact that the adrenal cortex is simultaneously eliminated. Thus, Swann and Fitzgerald<sup>23</sup> showed that in rats the removal of the adrenal medulla increased insulin sensitivity only twice, whereas removal of both parts of the adrenal increased it 24 times. Hence, the adrenal cortex appears far more intimately involved in insulin antagonism than is the medulla. The role of the endocrines in the regulation of the blood sugar has been well stated by Soskin<sup>24</sup>. This author maintains that the output of sugar by the liver is to a certain extent controlled by the sugar present in the hepatic cells even in the absence of any possible endocrine adjustment. In addition to this intrinsic hepatic mechanism and its endocrine regulations (anterior pituitary, thyroid and adrenal cortex) there are also certain emergency mechanisms

unquestionably supports the view that they result from potassium deficiency. These symptoms may persist even though the blood sugar has been restored to normal but yield promptly to the administration of potassium salts orally or parenterally.

The mechanism underlying the decline in serum potassium after insulin is still a matter of discussion. In diabetic acidosis and coma, potassium may be lost in the urine in excess as a result of tissue breakdown, glycosuria, diuresis, etc.<sup>5,41</sup>. When insulin is given to combat the acidosis, a shift of potassium from the extracellular fluids into the cells and liver occurs. This migration of potassium may be correlated with the effect of insulin on the oxidation of sugar, formation of intermediary carbohydrate-phosphate compounds<sup>51</sup>, glycogenesis<sup>37</sup> and the resynthesis of tissue proteins<sup>41</sup> since potassium ions are required in all these processes. Furthermore, the drop in serum potassium during the period of recovery from diabetic acidosis may be due in part to a number of other factors such as the use of large amounts of fluids, saline and in some instances bicarbonate and glucose. All workers, however, agree that insulin undoubtedly plays an important part in lowering the serum potassium even though this effect may not be a direct one. Frenkel et al.<sup>41</sup>, for instance, pointed to the compensatory secretion of epinephrine or some adrenocortical hormones as possible factors.

The clinical manifestations of potassium deficiency have been appreciated from earlier work in muscular paralysis, familial periodic paralysis, infantile diarrhea and chronic nephritis. Low potassium concentrations are thought to interfere with muscle metabolism and contraction<sup>109</sup>. However, just how potassium deficiency affects muscle metabolism has not been elucidated. It is conceivable that this phenomenon

involves some disturbance in the metabolism of acetylcholine. Mann<sup>81</sup> and Feldberg<sup>36</sup> observed that potassium ions increased the synthesis of acetylcholine and facilitated the release of this substance. Nachmansohn and Machado<sup>88</sup> showed that potassium was essential for the activation of the acetylcholine synthesizing enzyme, choline acetylase. Since acetylcholine is necessary for the conduction of nerve impulses and their transmission across the synapse and myoneural junction<sup>17,87</sup>, it is conceivable that potassium deficiency by inhibiting the synthesis as well as the release and removal of acetylcholine may result in muscular weakness and paralysis.

In most cases of diabetic coma, the potassium deficiency syndrome is absent<sup>41</sup>. Furthermore, the syndrome may account for only a small proportion of symptoms observed in severe or fatal hypoglycemia. Thus, potassium deficiency seems to be of only secondary importance in the production of the less severe hypoglycemic reaction. In this connection, it is of interest to note that the symptoms of potassium deficiency bear some similarity to those described by Himwich<sup>54</sup> as occurring in the last phases of hypoglycemia. Since at this point, neither glucose nor oxygen is any longer effective, Himwich feels that soon after the myelencephalic stage has developed, hypoglycemia becomes irreversible. However, it is conceivable that some hypoglycemic reactions considered heretofore to be irreversible may be corrected by the use of potassium salts. Consequently, irreversible reactions would be represented mainly by those in which actual brain lesions from hypoglycemia render all therapy ineffective.

**Integration of Factors Involved in the Mechanism of the Hypoglycemic Reaction.** The recognition that a sub-

normal blood sugar was accompanied by a group of characteristic symptoms proved fruitful in laying down the foundation for our understanding of the hypoglycemic reaction. As a result of this concept, however, the idea was entrenched that the symptoms accompanying hypoglycemia must always be related somehow to an excess of insulin or to a decrease of the blood sugar. The occasional though not infrequent demonstration of discrepancies between the clinical and laboratory findings in hypoglycemia was at first disregarded. This was probably due to the fact that observers failed to project the implications of such observations into the sphere of general functional disturbances. The recognition that glucose was the main nutritive substrate of the brain and that an inadequate supply of this sugar by producing secondary brain anoxia might account for the clinical picture of hypoglycemia was a great step forward. Yet, it was clear that the mere lowering of the brain sugar, whether reflected in the systemic blood or not, could not produce hypoglycemic symptoms and that the only way in which such nutritional deficiency could evoke a reaction was by inducing alterations in the function of the brain cell. It was also clear that cellular function of the brain could not be explained solely on the basis of two biochemical events, namely, the utilization of carbohydrate and the uptake of oxygen. Other substances, e.g., calcium, were also essential and it was obvious that disturbances in the metabolism of these substances might

also disturb profoundly the enzymatic reactions in the neuronal cell. Similarly, cerebral anoxia *per se*, e.g., carotid sinus syndrome, heart disease<sup>31</sup> and cerebral arteriosclerosis, might by virtue of its interference with brain function produce the clinical syndrome. Moreover, it should be recognized that function is not synonymous with metabolism and that the function of the brain may be disturbed independently of nutritional or metabolic factors. Such considerations suggest that the clinical symptomatology generally recognized as the hypoglycemic reaction is (a) the expression of a disturbance in brain function, (b) that this disturbance is revealed in the distorted cerebral electroactivity and (c) that the disturbed brain function is the common denominator of all such reactions.

The interpretation of the hypoglycemic reaction on this broader background appears to be of practical importance. The recognition that a similar clinical end result may be obtained in a variety of ways might be helpful in distinguishing reactions due to factors other than hypoglycemia. It may also be helpful in understanding that when several such factors are operative in the same individual, the reaction threshold may become reduced and the character and the intensity of reactions may be greatly modified. Lastly, the concept is also important because of its therapeutic implications. It may enable the clinician to treat patients with spontaneous hypoglycemia and labile diabetes more adequately than heretofore.

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# NEUROLOGY AND PSYCHIATRY

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## PSYCHOTHERAPY: AN ORIENTATION FOR NON-PSYCHIATRISTS

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Addressed to non-psychiatrists, this paper seeks to review in summary the more practical aspects of psychotherapy as they presently apply to the private practice of medicine and surgery. Admittedly fraught with sins of oversimplification, unwarranted generalization, and omissions, such an approach is vulnerable to attack by both psychiatrist and organicist. If, however, orientation in a confused terrain is furthered, the overworked plea of expediency may be justified.

Too much popular emphasis has plagued us *via* printer's ink, Hollywood celluloid, and radio scripts to make it necessary for this writer to demonstrate the ubiquity of psychopathology in our culture. The prevalence, at least, of psychopathology is evident. But we hear much, too, of "atomic" fission and its potential military application to abbreviate our life expectancies. Clearly, one may recognize the existence of a lion one has by the tail—yet remain quite unprepared to let go with safety. Private practitioners repeatedly find themselves in such an unsolicited and unapplauded role; *viz.*, being confronted by a patient whose illness may be far more readily identified as psychogenic than treated as such—either directly or by referral.

Among the barriers to optimum management may be arrayed a distrust or unfamiliarity on the part of the physician concerning psychotherapy, the practical (geographic and economic) difficulties of referral to a psychiatrist when indicated, and insufficient insight on the part of the patient into the psychogenic nature of his illness.

TO REFER OR NOT TO REFER? Studying his patient with predominantly "functional" symptoms, the physician may logically ask himself, "Shall I best serve this patient by symptomatic therapy and common sense advice, or by referral to a psychiatrist?"

One may say that the decision rests upon "clinical judgment" in reference to the specific case. True, but we use the phrase often to account for intuitive selection. Intuitive judgment, born of clinical experience, plays at least as significant a role in therapeutic management as it does in the diagnosis and the *art* of medicine as a whole. But if we affect a scientific basis for what we do, intuition—however valuable—must continuously lend itself to conversion into rational principles as our knowledge increases. Principles, not intuition, lend themselves to objectification, revision, pedagogy, and broadening practical application.

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Or one may decide to refer to the psychiatrist all patients with handicapping psychiatric symptomatology, at least all such patients who fail to respond promptly to simple reassurance and palliative medication. Were referral economically and geographically possible in each case, were there enough psychiatrists to go around, and were one's patients willing to be placed at the tender mercies of the psychiatrist—even then such a policy would be wasteful of the patient's resources and the physician's training. Not all these patients are curable, nor is specialty psychiatric care necessarily the most successful, broadly considered.

Denker<sup>8</sup>, for example, concluded from a survey of 500 disability insurance claims for psychoneurosis treated with superficial therapy by general practitioners, that the duration of disability and percentage of improvement or cures showed "no significant difference in the therapeutic success obtained by practitioners, psychiatrists, or psychoanalysts" (comparing his statistics with those reported in the literature by specialists). He felt from his study "that most psychoneuroses, as do many other diseases in medicine, run a self-limited course, and that the 'time factor' is of the greatest importance. The common sense and judgment required in intelligent treatment of this condition can be as effectively provided by the capable general practitioner as by the psychiatrist."<sup>\*</sup>

"Finally," as Groom<sup>14</sup> remarks, "there is something to be said for (psychotherapy's) downright interest, for a patient's mind can be as interesting as his colon."

The following considerations, though mutually interrelated, are discussed separately for convenience in attempting to objectify the often more or less

intuitive criteria by which one may decide for or against referral of his patient to a psychiatrist:

1. **Diagnosis.** Certain nosologic entities seem by their nature to demand specialized attention; *i.e.*, are otherwise unapproachable or too hazardous to justify palliation or brief psychotherapy by the non-psychiatrist. Psychoses, acute or chronic, are of this category because they usually require (a) potential closed ward security for protection against irresponsible injury to self and others, and (b) intensive treatment at minimum risk to render the personality accessible to psychotherapy (*e.g.*, electro-convulsive therapy, insulin shock therapy, hydrotherapy). These include disabling schizophrenia, or schizophrenia with active delusional systems; major deviations of mood (depression, elation, cyclothymia). Organic psychoses (*e.g.*, toxic deliria, general paresis, senile dementia) when severe usually require closed ward psychiatric management for safety and maximum benefit. Psychoneuroses, when (a) severe or acutely disabling (*e.g.*, reactive depression, panic, disorganizing anxiety reactions, certain hysterias), or (b) too chronic and inaccessible for conservative management (*e.g.*, obsessive-compulsive-ruminative neuroses, chronic invalidism, psychogenic asthma) may require referral.

Conversely, the non-psychiatrist has distinct advantages of rapport and flexibility in symptomatic management of many acute hysterias, mild and moderate anxiety states, and certain of the psychosomatic disorders (*e.g.*, peptic ulcer, essential arterial hypertension, "mucous" and "spastic colon" syndromes). He sees them earlier in their genesis, in the context of situational dissatisfactions and still blissfully free

<sup>\*</sup>Despite Dr. Denker's careful defense of the acknowledged margin of error in such a study, this writer finds it hard to accept the validity of his conclusions from comparisons among widely variant sources and clinical criteria, especially in view of the inevitable automatic selection of cases for (a) insured disability, (b) specialty psychiatric management, and (c) psychoanalysis. The data are nevertheless regarded as of sound illustrative import.

of the social stigma of being "mental."

2. **Severity.** Generally speaking, the more severe the personality distortion and functional disability, the more pressing is the demand for intensive treatment and rapid resolution of symptoms. The hazard of self-injury or impulsive action increases (within limits) with severity, as does the risk of personality rut-formation, hopelessness, regression, social and therapeutic exile.

3. **Prognosis.** Estimating prognosis in psychiatric illnesses propounds one of the most unsatisfactory and elusive tasks in all of medicine, depending as it does upon multiple and interrelated variables—not only existent within the patient and inherent in the illness, but also at the mercy of a changing situational milieu. But however non-committal the physician may try to be in discussions with patient and relatives, he must consider at least privately the

possibility and practicality of effective treatment, and usually must give the patient and others some rough prediction on which to plan. Other factors conforming, he may elect to retain for corrective treatment those patients with reasonably good prognosis, and those with such poor prognosis that only supportive and palliative care are indicated. In the latter event, of course, he is often wise to seek a psychiatrist's confirmation, if only to share the dissatisfaction arising when partial or no symptomatic relief can be obtained in management. Those patients with only fair or doubtful prognosis, or good prognosis only with intensive psychotherapy, are best handled by referral for specialized treatment.

A review of the following factors can be of some assistance in prognostication—within considerable margins of error:

#### A. History of past performance:

##### 1. Favorable:

- a. Average or better school work, social and marital adjustments preceding the onset of the illness.
- b. Consistency in effort, goals, standards—but not to the extent of rigidity or perfectionism.
- c. Failures and illnesses only in relation to *severe* stress (*e.g.* the soldier who broke down in severe and sustained combat, as opposed to the inductee who developed analogous symptoms during basic training).

##### 2. Unfavorable:

- a. Early and/or repeated emotional illnesses during life, in response to minimal or average stress.
- b. "Neuropathic" traits in childhood, especially if sustained; evidence of developmental anxiety during formative years (*e.g.* enuresis, excessive nailbiting, tantrums, phobias).
- c. Impulsivity in school, work, social behavior.
- d. Insidiously developing psychopathology.

#### B. Current personality factors:

##### 1. Favorable:

- a. Evidence of basic maturity.
- b. Strong therapeutic motivation (anxiety, aggressiveness, future goals).
- c. Rapport with physician.
- d. Insight (acceptance, at least, of psychologic mechanisms related to symptoms or coincident thereto).
- e. Average or better intelligence.
- f. Broad fund of experience and interest.

## 2. Unfavorable:

- a. Marked immaturity.
- b. Apathy, indifference to illness, self-centeredness.
- c. Delusional content; unrealistic and autistic thinking.
- d. Preoccupation with organic symptoms.
- e. Narrowed intelligence, interest, and experience.
- f. Evidence of "neuropathic" traits (nailbiting, tics, stutter, etc.).
- g. Incongruous affect or unaffected biologic rhythms in contrast to severe symptomatology.

## C. Situational factors: Prognosis proportionate to:

1. Capacity for insight, modification on part of relatives, associates.
2. Alterability of anxiety-producing stress and dissatisfactions (economic, interpersonal, etc.).

**Know thyself.** Psychotherapy presupposes on the part of the physician a working awareness of psychodynamics, acquired intuitively, experientially, and/or through specialized training. A working knowledge, too, of psychotherapeutic tools is prerequisite to flexible and efficient utilization of the potential opportunities for treatment. But equally significant are certain personality qualities of the physician himself. Psychotherapy, almost by definition being "relationship" therapy of patient by the doctor, the temperamental attributes of the therapist become powerful assets or liabilities in treatment—awareness of which in reference to the patient at hand may well determine whether the patient should be retained for treatment or referred elsewhere.

Although addressed to psychiatrists, the remarks attributed to Bartemeier<sup>4</sup> might well be applied to all physicians who include psychotherapy in their practice: "It is not given to all men by virtue of their childhood, adolescent and adult experiences, even though they have the necessary scientific background, intelligence and ordinary social gifts, to have the capacity for empathy. Successful psychotherapy presupposes . . . a certain feeling of conservative optimism, an ability to put one's heart into a problem yet have the courage

to say so when a problem is beyond one's capacities. The psychiatrist must not have too many conflicts of his own. He must make sure that he is straightened out with himself before he tries to help other people." A deft manipulator of the scalpel, for example, may or may not be equally facile in the manipulation of his own personality for the treatment of others.

A comfortable recognition of the time factor in psychotherapeutic management is of the greatest practical importance (Billings,<sup>5</sup> p. 224). One must be willing to allow interview time of one-half to one hour per session when indicated, often over periods of weeks or months. One must learn to be content with gradual and partial successes, the pace and degree of which are almost as little within the voluntary control of the patient or the doctor as is the constitutional resistance which effects a remission of pulmonary tuberculosis. Rogers,<sup>24</sup> writing of his management of tension states in general practice, counsels that the physician must have an attitude of "objective noncritical listening," in which the patient can discover for himself what his emotional conflicts are. The patient must feel free to work out his conflicts and solutions for himself." Rogers admits that this "is time consuming, but it is not all to be done at once. Were

the shortness of breath and palpitation due to pernicious anemia the illness would not be diagnosed or cured at one sitting."

In other words, he who essays practicing rational psychotherapy must recognize his own attitudes and personality structure as a part of the functioning therapeutic situation; notably, the physician's own sensitivities, tolerance, willingness to spend time, and reasonable patience in playing a passive listening role when required. On the other hand, it is not suggested that successful psychotherapy requires a physician of unsullied personality (provided he knows and allows for his quirks), unlimited time and inanimate mien. It is not meant to imply that the majority of cases require months of therapy, although a willingness to spend this long if required is desirable. Actually, the average acute anxiety or tension state which one sees in general practice requires about three or four interviews at the most for immediate relief.

Nor should the non-psychiatrist infer too exaggerated a concern about the "risks" of his performing occasional psychiatric management. It is the writer's opinion that the alleged "risks" of psychotherapy by non-psychiatrists are grossly overemphasized, provided the therapist is at least more of a listener than a judge, and is content to leave in the hands of the patient the initiative for probing into painful areas. Panic and acute psychotic reactions *do* result from heavy-handed direction or from premature exposure by the therapist of conflict-ridden areas (no matter how correct the interpretation); but even this is infrequent and can usually be averted by the timely recognition of stormy weather and prompt reversion to palliative reassurance or "non-directive" aeration of the disturbing content.

The common-sense avoidance of bulldozer approaches in psychiatry is no

more mysterious than it is in orthopedics. One does not test the initial movement of a partially ankylosed joint with active flexion—the patient is encouraged to find the limits of his own endurance, even cautioned to stop short of the absolute limits. Giving his qualified endorsement to a passive therapeutic attitude, Whitehorn<sup>26</sup> points out that the psychiatrist is thereby restrained from the too hasty and meddling projection of his own prejudices and presuppositions into the patient, and is more ready to grant the patient spontaneity and opportunity for expression: "Many of the harmful errors in 'over-active' therapy arise from a domineering attitude and from the uneasy and artificial necessity of playing Jehovah to the patient." "Yet much foolish delay and pernicious distortion of issues is also perpetrated in the name of passivity." Whitehorn adds that it is his "strong impression that the development of the therapist's most effective style of 'passivity' comes through much experience . . . because many patients, bit by bit, thoroughly convince the therapist of their own contribution to therapy and thus cultivate in him a very genuine respect for them."

**Which psychiatrist?** Members of the medical profession are prone to regard archly the irrational bases upon which laymen choose their physicians (not to mention their cultists). Yet our own referrals to specialist-colleagues are frequently only slightly more considered—based often upon the outcome of previous, dissimilar referrals; upon habitual contact with particular consultants; and sometimes solely upon their technical training and prestige. The choice of a psychiatrist—at least in larger communities where a choice is possible—brings into bold relief the importance of selecting the specialist to fit the patient. Successful psychotherapy may well be more dependent upon the aptness of the specialist's

personality, interest, and approach than upon his formal training.

As in any field where progress is occurring and where many questions must yet be answered on the basis of opinion, psychiatry is practiced by men who are united generally upon a broad base of theory, but who differ widely in its practical applications (*e.g.*, in therapy). Happily, at this writing, the schisms between mutually repellent "schools" of psychotherapy are progressively narrowing, as evidenced by Alexander's and French's<sup>3</sup> pragmatic adaptations of psychoanalysis to brief therapy, and by Masserman's<sup>21</sup> efforts to integrate inductively Myerian (psychobiologic) and Freudian (psychoanalytic) principles into a "Biodynamic theory of behavior." But even were the academic differences universally resolved, significant differences of interest, facility, and temperament would remain among individual psychotherapists. The day has long since passed when psychiatrists were exclusively found (practicing) within the walls of mental institutions. Specialty board certification in psychiatry endorses men whose proficiency varies from pediatric psychiatry to schizophrenia. One man may achieve brilliant results in the treatment of psychoses with insulin and electro-convulsive treatment, yet lack the patience and personality qualities for success in the treatment of psychoneuroses—and *vice versa*. To the general practitioner (who must survey the entire gamut of medicine) these nuances and sub-specialties may well seem hypothetical and unnecessary—annoyed, he may attempt to find one psychiatrist with universal aptitudes, or else insist that it is the psychiatrist's job to adapt himself to the patient ("After all, psychiatrists tell their patients how to adapt"). Nevertheless where choices exist, both extremes are unrealistic and as wasteful as referring a patient with brain tumor to a competent chest surgeon.

The sub-specialty of psychoanalysis requires particular mention because of its profound theoretical influence upon all psychotherapy, and because of its rather specific applicability—despite the multitude of popular misconceptions about Freudian methodology and rationale. Inductive and "microscopic" in its approach to the study of personality, classical psychoanalysis is the most scientific, least practicable psychotherapeutic discipline. To its theory and research we owe a great share of our concepts of the structure of personality, the psychodynamics of illness and health, and the rationale of psychotherapy. But "standard" psychoanalysis as generally practiced is unfortunately an unwieldy implement, beyond the reach of all but a minute fraction of psychiatric patients because of (a) the cost (rarely less than \$2000 annually), (b) the time (roughly, 18 months to 3 years; one-hour interviews daily, weekly, occasionally monthly), (c) the shortage of qualified psychoanalysts, and (d) often (appropriately) strict criteria of "treatability." Its application classically is analogous to radical surgery—justified in private practice when conservative therapy is ineffectual, but not when prognosis is hopeless. It has been estimated that less than 10% of psychiatrists' patients merit trial analysis, and of these only a few can continue (*i.e.*, have the requisite personality requirements and the practical opportunity to do so).

Still in experimental stage, and apparently actively opposed by a majority of psychoanalysts, are efforts to modify the classical Freudian discipline by planned, abbreviated therapy in which the therapist plays a more active and directive role<sup>3,21</sup>. Alexander<sup>3</sup> points (pp. 5-6) the direction of this development when he urges a "plan of treatment" and the "*conscious use of various techniques in a flexible manner*, shifting tactics to fit the particular needs of the

moment . . . using not only the method of free association but interviews of a more direct character, manipulating the frequency of the interviews, giving directives to the patient concerning his daily life . . . and making use of real-life experiences as an integral part of the therapy."

When compelled to select a psychiatrist in a locale where he has no personal contact, the referring physician must rely upon directory information; *viz.*, directories of local, state, and national medical associations; directories of specialists (diplomates of the American Board of Psychiatry and Neurology; affiliates of the American Psychiatric Association, and of regional and subspecialty associations). While a poor substitute for direct acquaintance, a knowledge of the consultant's training, academic affiliations, and emphasis in practice are of aid. Certification by the Board of Psychiatry and Neurology (in psychiatry or both) or membership in the American Psychoanalytic Society is evidence of both didactic and training requirements having been fulfilled in those fields.

**Economics of psychiatry.** Something must be said in defence of the alleged "expensiveness" of psychiatric treatment—even at the risk of gross overgeneralization from personal observations. Based on the total cost per patient-illness, it is indeed expensive in long-term cases—a crushing blow to the patient who is in even moderate circumstances. Still more overwhelming is the burden when disability and hospitalization supervene; worse if the patient has already run the gauntlet of diagnosis and therapy "by exclusion" with psychiatric intervention deferred as a last, desperate resort.

But a glance at tabulations of comparative incomes among physicians discloses neuropsychiatry as falling well below the mean, usually at or near the lowest income brackets of the pro-

fession—consistently below that of general practitioners, regardless of time in training. The cause of this seeming paradox (patient expense *vs.* doctor's income) is, of course, *time* and *volume* of patients. Only rarely can a psychotherapeutic interview be effective in less than one-half hour, and more usually an hour is required, with longer periods required for special examinations. Thus the psychiatrist's case load rapidly reaches a ceiling, his time saturated with a third or less the average number of daily patients, and his total cases per year necessarily limited because of the chronicity and spacing of treatment for each. Another economically significant characteristic is that psychotherapy can rarely be delegated—at least in private practice—to an assistant (associate, psychologist, social worker) or to a nurse. This is in direct contrast to the manipulative and pharmacologic ancillaries helpful in organic therapeutics.

Fees for psychotherapy in certain metropolitan centers have been observed by the writer to approximate \$15 to \$25 per treatment hour for pay-patients, with the lower figure rather consistently maintained for those in middle-income brackets. On the basis of *treatment time*, it is evident that the fees for psychiatric care are quite comparable to the \$3 to \$5 which a non-psychiatric patient would expect to pay for an ordinary office visit, as one of the several patients seen in that hour by the doctor. Fees for psychiatric management in hospital are less standardized, but it is doubtful that the psychiatrist's share exceeds that of the internist, and very likely falls well below the hospital fees of an active surgical practice.

These justifications, naturally, do not ameliorate the problem of economics for the psychiatric patient, who must nevertheless subsidize a greater proportion of the doctor's time than if he were afflicted with pneumonia or

a fractured femur. Their recognition, however, can orient the referring physician for practical advice to his patient, and can help the patient to understand the realities of private psychotherapy—thereby protecting rapport as well as public relations for private medicine as a whole. For patients of restricted and lower income brackets—even though capable of ordinary private medical care—it is usually more constructive and foresighted to encourage acceptance of treatment at tax-supported psychiatric facilities (mental hygiene clinics, child guidance clinics, teaching hospitals, state facilities) where available, than to press private psychotherapy in disregard of the additional stress which is ultimately created for the patient financially.

**THE NATURE AND AIMS OF PSYCHOTHERAPY.** Psychotherapy, as connoted in this discussion, may be defined as *any therapeutic effort to improve by psychologic means the patient's adaptation to reality*. Thus, *therapeutic efforts* can range from direct personality training to the fostering of healthier factors in the patient's life-situation (e.g., attempts to alter the attitudes of relatives, to aid in the solution of environmental problems. *Psychologic means*, broadly interpreted, implies major (but not exclusive) reliance upon personality function as an instrument of treatment, as opposed to primarily somatic procedures; operating through the influence of the therapist in his relationship with the patient and the latter's milieu. In *improving adaptation to reality* one must measure progress not only by more efficient and constructive behavior, but also by the reward of a fair share of gratification. *Reality*, of course, includes psychologic, biologic, environmental, and inter-personal factors (Alexander and French,<sup>3</sup> pp. 8, 11, 14, 18, viii).

Prerequisite to efficiency is the abandonment of neurotic goals<sup>26</sup>, and

the achievement of that tenuous and relative state of "maturity." Levine<sup>18</sup> itemizes (p. 286) some criteria which are helpful in measuring the degree of *emotional maturity* (especially in contrast to neurotic character-formation):

(a) ability to be guided by reality rather than by fears.

(b) use of long-term values.

(c) grown up conscience.

(d) independence.

(e) capacity to "love" someone else, but with an enlightened self-interest.

(f) a reasonable dependence.

(g) a reasonable aggressiveness.

(h) healthy defense-mechanisms.

(i) good sexual-adjustment with acceptance of own gender.

(j) good work-adjustment.

Elimination of undesirable attitudes and symptoms, of unrealistic goals and immature behavior must not, however, be assumed as the sole objective of psychotherapy—any more than the excision of diseased organs can be regarded as a sufficient guarantee of health. The psychiatrically ill patient is, in fact, in desperate need of replacements when his pathologic symptoms have been denied him or rendered no longer tenable. Frank,<sup>12</sup> for example, insists that if neurotic behavior is conceived as adaptive to situations perceived as threatening, into which the individual has no insight, then removal of the neurotic symptoms is of little value so long as the personality remains "saddled with the original conflict." If psychotherapy can not *replace* the neurotic symptoms with healthier patterns of behavior through reorganization of the personality or its function, we must then be content to minimize the handicap of functional symptoms—which symptoms, though pathologic, at least constitute a working mechanism of adaptation. It is both harmful and futile to insist righteously upon the removal of all protective symptoms unless there is prospect of the patient's

accepting a healthier alternative.

In addition to the realistic acceptance of *relative* success in psychotherapy (consistent with the patient's ability and practicality), it is useful to separate treatment tasks into what Whitehorn<sup>26</sup> categorizes as "major psychotherapy" (procedures directed toward overcoming the repetitive tendency of psychoses and severe neuroses), and "minor psychotherapy" ("procedures appropriate to the brief psychiatric episodes in which the patient's natural resources suffice for recovery with only minimal assistance"). This done, one is better prepared to select those particular therapeutic devices most appropriate; a number of which are reviewed below.

#### TOOLS OF PSYCHOTHERAPY.

1. **Radical techniques**, not applicable to non-psychiatrists' use. Certain techniques for intensive therapy are not feasibly adapted to use by non-psychiatrists, because of the hazards involved, the special training required for effective utilization, the need for special facilities and available psychiatric hospitalization in the event of acute psychotic reactions, and the time factor. They are reviewed here briefly for orientation:

(a) **"Shock" therapies.** Although not strictly psychotherapeutic in themselves, these procedures facilitate psychotherapy, and without the latter are often ineffective or of transient value. Their neurophysiologic mode of action is unknown, but they may be thought of functionally as useful in "fragmenting" certain fixed and pathologic associational patterns of thinking and emotional behavior, through the intervention of violent cortical excitation and unconsciousness. A secondary, purely psychologic, effect may be of significance; *viz.*, the satisfaction of a need for punishment in expiation of unconscious guilt.

Electro-convulsive therapy has displaced metrazol-induced convulsions because of the former's greater safety, convenience, and comfort; but carries about the mortality of a general anesthetic in addition to the occasional morbidity of long-bone fractures, mild vertebral compressions, muscular and ligamentous sprains. Curare can lessen the risk of fractures and dislocations in cases of known skeletal weakness, but adds the hazards of myocardial weakness and respiratory failure.<sup>16</sup> (Kalinowski and Hoch,<sup>16</sup> p. 150). Preliminary sodium pentothal narcosis has greatly reduced the anticipatory anxiety of treatment and the annoying confusion of recovery. Currently experimental use of uni-directional current and asymmetric placement of head electrodes gives promise of reducing the violence of initial convulsions, and the secondary confusion, respectively. Electro-convulsive therapy is indicated in functional (non-organic) psychoses; it is more reliable for the affective (mood deviation) psychoses and acute schizophrenic reactions than for the more chronic, insidiously developing psychoses (*e.g.*, chronic paranoid and hebephrenic schizophrenias). Its use in psychoneuroses and immaturity reactions is generally condemned, being justified probably only when these syndromes are so severe as to present a stage of rut-formation approximating psychotic deviation, thus rendering the patient otherwise inaccessible to psychotherapy.

"Pure" affective (mood) disorders require usually ten or less electro-convulsions in all (usual frequency: 3 to 2 per week), whereas those disorders which include topical (thinking) disturbances usually require from ten to twenty treatments. In those rare psychoneurotic disorders which justify electro-convulsive therapy, usually six or fewer seizures will produce what



benefits are to be obtained. The actual number of treatments required irrespective of diagnosis, however, is determined by the cumulative effect upon the patient's mood, behavior, and insight; but rarely are more than 20 in a series justified. As improvement occurs most psychiatrists prefer to space the treatments at increasing intervals (from 3 to 2 or 1 per week), discontinuing entirely for observation when symptoms have largely cleared. By the time a patient has had no relapse over a period of 2 or 3 weeks without treatment, electro-convulsive therapy can be discontinued altogether, a late relapse then being unlikely. The confusion and amnesia for recent memories, which are a cumulative side-effect of electro-convulsions, begin to clear as treatments are spaced more than 3 days apart, and are as a rule dissipated within 3 weeks of the last treatment. Treatments may be given in hospital either on an in-patient or out-patient basis, depending upon the adequacy of home care, the patient's cooperativeness, and the degree of confusion and mood-swings attending treatment. During the course of electro-convulsive treatment, intensive psychotherapy is feasible only early in the series and subsequent to about one week after completion, because of the retention defect described.

**Insulin shock therapy** (in contrast to tonic or sub-shock insulin) has been used almost exclusively in schizophrenic disorders, particularly those of more insidious development, refractory to electro-convulsive treatment, and characterized by fixed delusional or hallucinatory systems. Its use alone has become less common with the development of electro-convulsive therapy, but is still of value in combination with the latter for refractory cases of poor prognosis. Deep insulin therapy has the disadvantages of somewhat greater hazard

(mortality and morbidity), requiring prolonged hospitalization and expert nursing care, and considerably more conscious discomfort than electro-convulsive treatment. The frequency and duration of treatment vary widely, but often a total of 40 to 80 comas (1 daily for 6 mornings weekly) with electro-convulsions interspersed during the initial weeks (2 to 3 times weekly at the height of coma) are considered desirable.

(b) **Continuous sleep therapy** has been tried in past years intermittently without striking success, compared to other methods. To date it does not appear to offer any substantial advantages over the "shock" therapies, and its results seem too unpredictable and insufficient to outweigh the hazards and difficulties of administration.

(c) **Frontal lobe neurosurgery.** Pre-frontal lobotomy, leukotomy, and topectomy are, again, not strictly psychotherapeutic measures but are of interest here as surgical recourse for patients of otherwise poor prognosis who have failed to respond to other types of radical therapy. Remarkable results from such surgery have included the conversion of intractably agitated patients into placid individuals suitable to return home, and "deteriorated" backward psychotic patients into relatively self-sufficient cases requiring less custodial care. Unfortunately the results at this writing are widely variable and unpredictable. Since the results are irreversible and the mortality appreciable, frontal lobe surgery for the time being should continue to be restricted to those cases of near-hopeless psychotherapeutic prognosis.

(d) **Intensive personality analysis.** This includes psychoanalysis and Myerian "distributive" analysis, as well as many intermediate schools of therapy. For purposes of this discussion the first

two mentioned are most useful as representative psychotherapeutic disciplines, both of which require special training and organization of time which place them outside the practical reach of the non-psychiatrist. Classical psychoanalysis has been referred to earlier in this paper. Myerian "distributive" analysis stresses psychobiologic integration (the individual as a whole),<sup>23</sup> and distributes analysis selectively along lines of particular personality difficulty, as well as laying heavy emphasis upon socio-economic factors and the total life situation (Diethelm,<sup>9</sup> p. 111). Synthesis of personality assets accompanies the analytic procedures as data and insight accumulate, with the goal being a more purposeful psychobiologic adaptation to the total life situation (Billings,<sup>5</sup> pp. 234-239). Compared to classical psychoanalysis, it is evident that psychobiology presents a somewhat less inductive, more pragmatic methodology—having the disadvantages of less standardization, multiple variables, and probably being less objective as a scientific discipline; but having simultaneously the advantages of more flexibility, pragmatic expediency, and lending itself to specific application with the resultant saving in time for at least functional cures.

As mentioned, between these representative approaches to intensive psychotherapy lie many variations of technique and theoretical emphasis, including the experimental projects under way apparently leading to utilization of the contributions of both psychoanalysis and psychobiology.<sup>3,21</sup> As yet, the multiplicity of views and disagreements is testimony to the existence of an uncharted area between theory and practice of psychotherapy, making it more important to rely upon the selection of a man appropriate to the patient rather than to over-value the consultant's theoretical views. The differences are by no means as wide in the actual

practice of psychotherapy as they appear to be in polemics on theory.

(e) **Hypnosis** is included in this section not because of any intrinsic difficulty or hazards in its practice with reasonably stable personalities, but rather because of the risk of precipitating occasionally a psychotic panic or involving the physician in a previously unrecognized delusional pattern. Because an unrecognized schizophrenic development may masquerade as a simple hysteria or anxiety reaction, the practice of hypnosis by non-psychiatrists is to be discouraged. As will be mentioned below, if a short-cut to analysis and synthesis is needed to circumvent conscious or pre-conscious resistance, it is this writer's opinion that narcosis interviews (with sodium pentothal or sodium amytal intravenously) are psychotherapeutically safer and more productive in the hands of the non-psychiatrist. Should a panic or psychotic reaction then be released during narcosis interview, one can at least control the emergency promptly (and probably render the patient essentially amnesic for the incident) by inducing full sleep.

**2. Conservative analytic techniques.** While these procedures are quite appropriate for the non-psychiatrist's use, provided he has the prerequisite interest and personality, they are used with more assurance when facilities are at least potentially available for psychiatric hospitalization in the event of an emergency.

(a) **"Non-directive" interviews.** As a term, this is probably a misnomer, since common-sense direction of a strictly limited sort is highly desirable. As discussed earlier in this paper, however the concept of passivity on the part of the therapist is one of the significant contributions of Freud to therapy, protecting the patient from standards and authority imposed arbitrarily by the doctor (which, if the patient accepts,

serve only to foster his dependency upon authority rather than to prepare him for independent solutions in the future). As Alexander<sup>3</sup> remarks, psychoanalytic treatment is a part of the patient's ego development—and not the doctor's "therapeutic act" upon the patient *via* interpretations. The same philosophy can be useful in non-directive psychotherapeutic interviews.

This approach requires, first of all, that the physician "listen out" the patient's story, although now and then mirroring back to the patient those statements which seem crucial or inconsistent—but scrupulously refraining from outright judgment or rebuttal. As discussion progresses, then, the physician may factually point out any obvious clues to emotional reactions associated with the subject at hand (tears, anger, flushing, hesitation, defensiveness, etc.), seeking to help the patient to accept openly his emotional attitudes as well as his stated problems. The therapist may summarize or (guardedly) interpret the patient's conclusions and attitudes—often in the form of a question—which serves to (1) demonstrate to the patient that his views are at least being recognized, (2) objectify the patient's assertions or denials by restatement, and (3) guide subtly the discussion by emphasis of selected material.

It may be protested that such passivity on the part of the physician is wasteful of his time and training—that the patient comes for help, not to talk until he stumbles upon his own answers. But this criticism, justified within limits, would also imply that the best teachers are those who solve the problems for their pupils. Corrective psychotherapy is, after all, a re-educational procedure—although as much concerned with the retraining of emotional patterns as of intellectual concepts. Socrates taught "non-directively;" *i.e.*, relied upon the assertions and conclusions of his pupils for material

which, through reinterpretation and adroit questioning by him, led his students to accept new principles on their own terms. "A man convinced against his will is of the same opinion still." Corrective psychotherapy requires of a physician that he be more a teacher than an authority.

In contrast to the more superficial devices of persuasion, direction, and reassurance (discussed below), non-directive psychotherapy is indicated for personality conflicts of deeper origin, the solution of which is dependent upon insight acquired by the patient himself as he maintains reasonable initiative in the quest.

(b) Narcosis interviews (narco-diagnosis, narco-analysis, narco-synthesis). Interviews under narcosis with sodium pentothal or sodium amytal administered intravenously have become a valuable diagnostic and therapeutic weapon,<sup>15</sup> having been given great impetus during the war by Grinker and Spiegel.<sup>13a</sup> Analogous to hypnosis but safer from a psychotherapeutic standpoint in non-psychiatrists' hands, narcosis interviews provide a means of diminishing conscious and pre-conscious resistance (*e.g.*, fear, embarrassment, anxiety) to the release of underlying thoughts and feelings, allowing their aeration without loss of prestige by the patient. In addition to the subjective relief often experienced by the patient therefrom, the physician is provided with data for later discussion with the patient as well as for his own evaluation of the etiology and prognosis. In puzzling problems of differential diagnosis, the behavior, content, and mood of a patient while near-somnolent frequently supply pathognomonic evidence of the underlying psychopathology. Thus, for example, an agitated patient may react to narcosis with (1) striking relief of all symptoms, implying a relatively superficial dis-

turbance; or (2) sustained mood of despondency and futility, with self-depreciatory content implying a deep-seated depressive disorder (affective psychosis or severe reactive depression); or (3) expose delusional and hallucinatory material indicative of a potential or actual psychotic disorder of thinking. It is not meant to suggest that all reactions under narcosis are this clear-cut, but the technique is unquestionably becoming of great diagnostic and prognostic significance when combined with other clinical data.

The use, by Grinker and Spiegel,<sup>13a</sup> of narco-analysis in combat reactions emphasized the production of emotional catharsis by suggestively recreating the traumatic combat scene for the patient and encouraging him to re-enact the episode verbally and physically—this being followed by suggestive reassurance as the interview was terminated. Probably because of the multiplicity of stresses in civil life and the more gradual development of anxiety reactions, Grinker's abreactive technique is usually not suitable for civil practice. Verbal aeration (with emotional but not physical abreaction) of conflicts and tension is usually adequate when narco-analysis and narco-synthesis are effective.

The technique of administration is not difficult but is safest in a hospital setting where nursing observation, oxygen-carbon-dioxide, and stimulants are available when needed. Sodium pentothal is conveniently administered in a 5% intravenous solution in distilled water (0.5 gm. or gr.  $7\frac{1}{2}$  in 10 cc.) and given slowly (1 cc. per minute) until drowsiness and thickness of speech are attained, then is given more slowly to maintain the desired stupor throughout interview. Tolerance varies from 0.2 gm. (gr. 3) to about 0.6 gm. (gr. 9), but close observation is imperative because of the occasional hypersensitivity to the drug. I do not believe

that more than 0.8 gm. is justified in a single interview, and if this amount is insufficient for narcosis the patient should be tried at a subsequent time on sodium amytal. Sodium amytal may be given in the same concentration as sodium pentothal but more slowly and injection terminated at a lighter stage because of sodium amytal's slower action and associated latent period before peak effect; after slight drowsiness and thickness of speech are observed, the needle may be withdrawn. The latent period ranges clinically from about 5 to 15 minutes, and the duration of adequate narcosis continues well beyond the length of the average interview. It is well to have parenteral stimulants (*e.g.*, "Desoxyn," picrotoxin, and/or epinephrine) available for use in event of too deep narcosis.

It is wise, also, for the physician to have assistance within call in the event that an uncontrolled agitation or psychotic reaction is precipitated; and, in the case of female patients, a nurse (in whom the patient has confidence) present in the room throughout narcosis. It is usually sufficient to assure the patient that he will experience a feeling of pleasant relaxation, in the course of which his tension will ease and he will find it easier to express his thoughts and feelings. If spontaneous aeration is insufficient or non-informing, production can then be guided by terse questions or suggestion, and the interview finally terminated with explanation and reassurance. Nursing attention serves to protect the patient from falling or otherwise injuring himself after interview is terminated and before somnolence has cleared (duration: 1 to 2 hours for sodium pentothal, 4 to 6 hours for sodium amytal). Mild doses of amphetamine derivatives are helpful in shortening the post-interview symptoms.

Narco-diagnosis usually requires only one interview; therapeutic narco-analy-

sis and narco-synthesis are more effective with at least 2, often 3 or more interviews, plus intervening discussions with the patient of content and affect released. Usually rapport is so much improved after one or more interviews that the patient can then voluntarily continue therapeutic interviews without (or with token doses of) a hypnotic. Certain patients are remarkably unproductive and tolerant of one or the other hypnotic agent; a trial of the alternative drug on subsequent interview often proves successful. A recent (and apparently unreported) modification of the technique seems very promising to increase productivity during interview; *viz.*, the simultaneous use of amphetamine derivatives (*e.g.*, "Desoxyn" 5-10 mgm. orally,  $\frac{1}{2}$  hour before administration of hypnotic).<sup>7</sup> While seemingly in opposition to the hypnotic, the stimulant results in much greater productivity during interview. Its use in narco-diagnosis, however, is probably confusing, since an underlying depression might be masked.

A useful evaluation of the present status of narco-diagnosis and narco-therapy has been contributed by Hoch.<sup>15</sup>

**3. Repressive-integrative techniques** (synthesis, support, persuasion, reassurance, direction). Procedures of this variety are so commonly used in all of medical practice that it would be pedantic to discuss them in detail. Obviously their appeal and efficacy are largely restricted to the patient's conscious awareness and controls, and they are primarily accepted upon faith in the authority of the physician. This is not to discredit their value but simply to emphasize that failures from their use can not reasonably be attributed either to (a) the physician's incapacity or misunderstanding, nor to (b) the patient's conscious unwillingness to accept advice. Failures will more likely

occur because the approach is confined to a relatively superficial level of behavior and can have little influence upon the deeper, personality-determined motivations.

Since it is primarily the psychoneuroses and immaturity reactions the physician will be treating with "covering" techniques, it is important to have some working concept of their general etiology. Alexander's<sup>3</sup> definition fits this purpose: "Psychoneurosis is a failure of the individual to deal successfully with a given situation, a failure to find socially acceptable gratification for subjective needs under given circumstances. This failure depends upon the balance between the ego's adaptability and the difficulty of the confronting problem. When the situation demands greater powers of integration than the ego possesses, a neurosis develops. Whether the ego became incapacitated in childhood, adolescence, or adult life, and how it is limited by constitutional endowment, are secondary questions."

The "secondary questions," of course, from the point of view of this present discussion are exceedingly important practically in therapy, since superficial treatment can alter little the personality distortions arising in childhood or adolescence—unless effectively applied during those periods.

Certain aspects of repressive psychotherapy merit specific mention:

(a) **Reassurance, explanation.** The physician to whom the patient first goes with his specific symptomatology has a peculiarly powerful influence on the patient's subsequent attitude toward his illness. To be effective, reassurance can not be prematurely voiced, but must await reasonably adequate (but not obsessive) study—whether the symptomatology is predominantly organic or "functional." Reassurance can be nullified simultaneously by the physician's denial of

(1) obvious handicaps, (2) the validity of the patient's symptoms (though not organic in origin), or (3) the possibility of slow and intermittent resolution of symptoms.

One can not reassure the patient simply by denying the presence of disease. Fortunately the laity has a legitimate distrust of diagnosis by exclusion; thus one should not attempt to stop with the denial of an organic basis for symptoms. It is imperative to give the patient some reasonable explanation for his symptoms (beyond "Just Nerves"): specific situational stress, history of previous somatic reactions to emotional trauma, mechanisms of "functional" somatic symptoms, etc. Unless we do this, we fall into the fallacies of the "buck up and forget it" school of "psychotherapy"—and become major contributors to the business of charlatans by driving patients from ethical medical care.

The use of bibliotherapy (selected reading for patients) has been disappointing, and is not without considerable risk to an anxious and non-critical patient. Probably the most innocuous but still psychiatrically valid book suitable for almost any patient (and family) is a popular best-seller written by a layman (Rabbi Joshua Liebman's<sup>19</sup> *Peace of Mind*). This is a simply written description of certain emotional conflicts and the psychoanalytic philosophy of treatment, plus an attempt to reconcile psychiatric principles with religion. For patients in relatively stable adjustment and of good intelligence (and especially for parents and teachers having these qualifications, and who complain of "difficult" children) a more informative book by English and Pearson<sup>11</sup> (*The Emotional Problems of Living*) has been of considerable help in providing insight into personality growth and architecture. Over all, however, "bibliotherapy" is a misnomer—bibliographic references

can be of prophylactic value to well individuals, but rarely are as therapeutic as they are disturbing to a psychiatrically ill patient.

Source-material for the physician, on the other hand, is relatively plentiful and of considerable value in providing him with a working knowledge of techniques, mental mechanisms, common misconceptions and pitfalls, etc., to aid in psychotherapeutic management. Although unfortunately widely scattered and presented in fragments, this information is well-formulated and available elsewhere<sup>3,5,9,10,11a,13,14,17,18,20,21,25</sup> and space does not permit a detailed review here.

(b) **Supportive measures.** Supportive care includes the use of such supplementary dietary and metabolic aids as are indicated by coexistent or related physical disturbances; plus reasonable attempts to restore more normal biologic rhythms (e.g., reduction of insomnia, constipation). If the interference with biologic rhythms is severe, hospitalization for more sustained initial observation and control of medication is highly desirable. Tonic dosage of insulin ("regular" insulin, 10 to 30 units depending upon tolerance,  $\frac{1}{2}$  hour before meals) for hospitalized patients is often of value through relief of muscular tension, increased appetite and utilization of carbohydrates, and a subjective feeling of well-being. Other pharmacologic applications to supportive therapy are mentioned separately below.

(c) **Manipulation of environment and activity.** Medical recommendations for temporary or permanent alteration of the environment are of occasional help, especially when a patient needs (1) assistance in altering habitual patterns of behavior, (2) temporary respite or concessions from a stress-producing environment, and (3) introduction to new fields of endeavor. These are generally palliative devices, however, ranging

from hospitalization to protect a patient from well-meaning relatives to the urging of hobbies. Their use is not without its pitfalls; notably the fallacy inherent in "rest cures" which are based, as Karl Menninger<sup>22</sup> reasons, upon the fatigue theory of neurosis. Psychiatric illness, he points out, is the result of misdirected energy rather than the lack of energy. Groom<sup>14</sup> remarks that physicians should occasionally examine their own motives for sending anxious patients (far) away on vacations.

(d) **Pharmacologic aids.** The use of pharmacologic support in psychosomatic disorders is often fraught with more hazards than benefits, but if a conservative attitude prevails on the part of the physician and he is careful to imbue his patient with the philosophy that medications are intended to *reduce* symptoms temporarily rather than to *obliterate* them, it is hard to deny patients the reassurance of the excellent pharmacologic armamentarium now available. Some of the more useful drugs for this purpose may be grouped as follows: (1) rapid, delayed action, or slowly acting sedatives; (2) amphetamine sulfate and derivatives of rapid-acting type, for morning and noon stimulation of depressed and lethargic patients—preferably combined with minimal doses of a barbiturate to reduce tension and side-effects of amphetamine; (3) antispasmodics of recent development, relatively free of atropine side-reactions, for spastic gastrointestinal and other vegetative dyskinesias; (4) antihistaminics for severer allergic manifestations; and (5) bulk-formers for the conservative control of constipation.

A few safeguards seem particularly required in the pharmacologic treatment of psychiatric patients, since many of these individuals are potentially dependent upon any "crutch"—whether the crutch be mechanical,

human, chemical, or institutional: (1) prescriptions for sedatives and stimulants should be non-renewable and for short periods (2 to 3 weeks); (2) sedatives, stimulants, and antispasmodics should be prescribed in almost homeopathic doses initially (except in emergencies), and the maintenance dose held at a very minimum; patients in the throes of anxiety frequently prove remarkably hypersensitive to even average doses; (3) alcohol, bromides, and narcotics have, in this writer's opinion, no place in psychotherapy except possibly when safer agents are not available for an emergency; (4) for older and arteriosclerotic patients, phenobarbital (or "Luminal") often produces unwarranted cerebral retardation and occasionally confusion; plain barbital, "Mebaral," sodium barbital, sodium amytal, paraldehyde, and the newer urea compounds are among the more desirable sedatives and hypnotics for these patients; (5) the use of hormonal substitution therapy (particularly gonadal) in cases of predominantly psychiatric symptomatology has been almost universally disappointing and scarcely justified (in the absence of gross organic indications) as an adjunct to psychotherapy; and (6) the availability of symptomatic remedies must not distract the physician nor his patient from the primary problem and the patient-as-a-whole, lest they be lost in a forest of symptoms with new distractions springing up as older ones are dampened pharmacologically or otherwise.

**SUMMARY.** Some of the present aspects of psychotherapy are surveyed for orientation of the non-psychiatrist:

1. Patients presenting mild to moderate psychopathology are often best treated by the non-psychiatrist, using proper criteria for selection and reasonable conservatism in the flexible use of psychotherapeutic techniques.

2. Successful psychiatric referral is heavily dependent upon the rational selection both of the patient as suitable and the psychiatrist as appropriate to the patient and his problem.

3. The referring physician plays a powerful role in determining the patient's attitude toward his symptomatology, as well as toward subsequent

psychotherapy. Some preparation of the patient for the latter before referral (*i.e.*, indications, rationale, practical problems related) can greatly facilitate successful psychiatric management.

4. Present trends in psychotherapeutic practice give promise of more pragmatic adaptation of previously divergent theories.

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PHYSIOLOGY  
PROCEEDINGS OF  
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA  
SESSION OF FEBRUARY 17, 1948

The Renal Elimination of Caronamide (4'-carboxyphenylmethanesulfon-anilide). HAROLD M. PECK, M.D., ELIZABETH K. TILLSON, WILLIAM S. WALLER and KARL H. BEYER, Ph.D., M.D. (Medical Research Division, Sharp and Dohme, Inc., Glenolden, Penna.). Caronamide (4'-carboxyphenylmethanesulfon-anilide) has been demonstrated to be an effective agent for the inhibition of the renal tubular excretion of penicillin. The hypothesis for such an agent provided that it reversibly inhibit the tubular excretion of penicillin by an affinity for the tubular transport mechanism involved and that it be eliminated essentially by glomerular filtration.

Experimental procedures for the study of renal elimination of caronamide in dogs have included the following: 1) Simultaneous plasma concentrations of caronamide and mannitol, over an 8-hour period, in bilaterally nephrectomized, unanesthetized dogs. 2) Simultaneous urinary recoveries of caronamide and mannitol. 3) Simultaneous falling plasma concentrations of caronamide and mannitol. 4) Clearance ratios, excretion ratios, and extraction ratios of caronamide obtained by comparing its clearances and extractions to those of creatinine.

Analytical methods included the colorimetric method of Ziegler and Sprague (J. Lab. Clin. Med., 33, 96, 1948) which measures caronamide per se and its metabolites and the method of Brodie, Levy and Bernstein (J. Pharm. and Exper. Therap., 91, 246, 1947) which measures caronamide per se. Correction for binding on plasma pro-

tein was based on results obtained by the method of Lovietts (J. B. C., 120, 267, 1937).

The results obtained justified the following conclusions: 1) Caronamide undergoes some alteration in the body that increases its water solubility but does not seem to alter the manner in which the kidney handles the drug. 2) Practically all of a dose of caronamide administered orally or intravenously is recovered as such, or in the form of metabolites, in the urine. 3) Present evidence indicates that caronamide and its metabolites are excreted by glomerular filtration. 4) The clearance of caronamide is inversely related to its plasma concentration. 5) Present evidence permits the tentative conclusion that bound, as well as unbound, caronamide contributes to the amount filtered, rendering a correction for binding an uncertain quantity of questionable significance.

Comparison of Two Types of Permanent External Bile-fistula Dogs for Studying Liver function. WILLIAM J. SNAPE, M.D., C. WILMER WIRTS, M.D., and ABRAHAM CANTAROW, M. D. (Depts. of Physiology, Medicine, and Biochemistry, Jefferson Medical College.) A tubulated duodenal fistula, of the type first described by Thomas, placed opposite the biliary ampulla was utilized to collect bile. This type of bile-fistula is compared with the Rous-McMaster fistula preparation. Some of the advantages of the Thomas-fistula dog are (a) it has a shorter period of convalescence, (b) requires no special diet or care, (c) survives for long pe-

riods of time, (d) maintains good liver function and freedom from extra hepatic obstruction. Comparing the two preparations it was found that all of the Thomas-fistula dogs met the criteria for normal bromsulfalein excretion in the bile, while only six out of twenty-two of the older type (Rous-McMaster) met these requirements. None of the newer type preparations showed any bromsulfalein retention while four of the five standard animals exhibited this abnormality. The volume of bile excreted per unit of time was almost identical in the two preparations. However, in general the older type fistula dog did not excrete as much dye as the Thomas-fistula dog. Therefore, it would seem that rather than an obstruction to the flow of bile actually these animals had liver impairment.

Comparing the 2 mgm./kilo dose and the 5 mgm./kilo dose of bromsulfalein we find the concentration in the bile to be enormously increased but the shape of the excretion curve and the concentration at the end of two hours are practically identical.

The preparation described has been found useful in comparing rates of excretion of various injected materials and evaluation of various choleretics.

**Variations in the Blood-supply of the Liver, Gall Bladder, Stomach, Duodenum, Pancreas and Spleen (200 dissections).**\* NICHOLAS A. MICHELS, Dr. Sc. (Daniel Baugh Institute of Anatomy, Jefferson Medical College). In my previous work (*Am. J. Anat.*, 1942) it was shown that in 100 bodies each spleen had a different terminal divisional pattern of the splenic artery. Total splenic arterial bed length varied from 30-90 cms., length of splenic from 8-32 cms. marked tortuosity), lienal branches from 7-35, some arising early

(distributed splenic), others late (magistral splenic).

Like the spleen, each liver has a different pattern of terminal arterial vascularization. In 52% the celiac hepatic supplies a right, left and middle hepatic, the latter a branch of right or left hepatic supplying quadrate lobe. The 3 main hepatic branches give off numerous terminal branches (20-65) each selectively distributed to a specific liver area as is readily observed when branches in the umbilical fossa are dissected.

An aberrant hepatic artery (one arising otherwise than from celiac hepatic) occurs nearly in every other body (48%). Aberrant right hepatics arise prevailingly from superior mesenteric; aberrant left hepatics from left gastric. Of aberrant right hepatics (22%), 15.5% were replaced right hepatics, i.e., the only right hepatic present; 6.5% were accessory right hepatics. Of aberrant left hepatics (26%), 14% were replaced left hepatics, 12% were accessory left hepatics. Predictable estimate: Nearly every other aberrant left hepatic from left gastric constitutes the only left hepatic present and 3 of every 4 aberrant right hepatics from superior mesenteric are replaced right hepatics. Entire hepatic trunk may come from superior mesenteric or left gastric.

Single cystic artery from right hepatic 58.5%; replaced types 16.5%. Double cystic 24.5%; one triple. Right hepatic ventral to hepatic duct, 14.5%. Accessory hepatic ducts, 14%.

Investigation showed constancy of four arteries usually not described in text-books: 1) retroduodenal (first br. of gastroduodenal) to back of duodenum and head of pancreas; 2) supra-duodenal to first part of duodenum; 3) dorsal pancreatic (from splenic, hepatic, celiac, sup. mesenteric); 4) trans-

\* Aided by a grant from the American Philosophical Society.

verse pancreatic, which courses along inferior surface of pancreas.

**Direct Experiments on the Interpretation of the Ballistocardiogram.** O. HORWITZ, M.D., R. L. MAYOCK, M.D., and ISAAC STARR, M.D. (Depts. of Therapeutic Research and Medicine, Univ. of Penna.) At the first stage of necropsy the aorta has been cannulated at the aortic valve. The cannula, bent at a 90° angle, was attached to a piston syringe. A Hamilton manometer was inserted in the aorta, and "diastolic" pressure maintained by saline solution running into the femoral artery from a bottle raised to the diastolic level. The subject lay on the ballistocardiograph and the position of the syringe plunger, and the blood pressure were recorded simultaneously with the ballistocardiogram by appropriate optical systems. "Systoles" of various types were obtained by pushing home the plunger by hand, or by striking it with a padded mallet. The records of 29 such systoles, obtained on two cadavers with normal blood vessels, aged 22 and 14 years, have been analysed.

The *shape* of the ballistocardiogram

depends on the shape of the ejection velocity curve; when the latter attains maximum velocity early in systole the ballistocardiogram is normal in form. Otherwise it is abnormal.

The *size* of the ballistocardiogram depends on the acceleration of the ejected fluid. The correlation between maximum positive acceleration and the area of I and J waves is +0.72, between maximum positive acceleration and the area of I + J divided by their duration is +0.84. The amplitude of the ballistocardiogram is, therefore, primarily related to the heart's force, and as the duration is known, to the heart's power. The relation to cardiac output is secondary.

Nevertheless the calculated values for cardiac output, adjusted for the lack of right sided effects by doubling the I wave area, agree fairly well with the actual. In only 8 instances was the ballistocardiogram normal in form and the pulse rate, calculated from the duration of ejection, between 43 and 200. In these, the average difference between actual and calculated stroke volumes was +1%, the standard deviation about this mean 13%.

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# BOOK REVIEWS AND NOTICES

TEACHING PSYCHOTHERAPEUTIC MEDICINE. Edited by HELEN LELAND WITMER, Ph.D. Pp. 464. New York: The Commonwealth Fund, 1947. Price, \$3.75.

THIS "Minnesota Experiment" has important meaning for every practitioner of medicine. Twenty-three physicians in general practice, a pediatrician and a dermatologist met 7 psychiatrists and 2 internists in an outpatient clinic where they worked and talked for 2 weeks—from 8:30 A. M. to 9 P. M.

Talks by psychiatrists on such topics as Normal Personality Development, Anxiety, Emotions and Disease were followed by informal section meetings and, most important, hour-long interviews between the physicians and out-patients. Sometimes a psychiatrist would come into the last minutes of an interview. In the second week some explanations of the psychoneuroses were given and illustrated by clinical examples and physiological demonstrations of the effects of emotion on body functions.

Appraisals of the value of this experiment are deservedly enthusiastic. Physicians to whom patients turn first in every kind of illness learned to deal with easily understandable methods of psychotherapy which were superficial but which could bring surprisingly good results. They learned also to recognize malignant mental conditions which were either to be let alone or referred to psychiatrists.

An invaluable contribution was made by internists Drs. Bauer and Wolff in fitting organic disease and the play of emotion into the life situations of patients.

This book is strongly recommended to all physicians. The Commonwealth Fund has scored a great success in this experiment.

E. B.

HANDBOOK ON FRACTURES. By DUNCAN EVE, Jr., M.D., F.A.C.S., Assoc. Prof. of Surgery, Vanderbilt Univ. Pp. 263; 129 ills. St. Louis: C. V. Mosby, 1947. Price, \$5.00.

THIS concise, little book on fractures is remarkably replete with the essential principles and is illustrated with very informative photographs and line drawings. It should be an excellent aid as a handbook in the teaching of fractures, representing a summation of more than 40 years in the field of fracture work by a busy and practical surgeon. Dr. Eve is to be congratulated.

P. C.

THE PATHOLOGY OF NUTRITIONAL DISEASE. By RICHARD H. FOLLIS, Jr., M.D., Assoc. Prof. of Pathology, Duke Univ. School of Medicine. Pp. 291; 71 ills. Springfield, Ill.: Charles C. Thomas, 1947. Price, \$6.75.

THE subject of nutritional disease has become so vast that it tends to be bewildering to one not closely connected with the field. Nevertheless, Dr. Follis has managed to condense the subject into a concise, readable volume. The pathologic changes in both experimental animals and in man are clearly described and well illustrated by copious photographs. Topics discussed include the essential elements, essential amino acids, and vitamins. For each substance, a brief historical review and discussion of biochemical relationships is given in addition to a description of pathologic changes. This volume should prove of value to both pathologist and clinician.

A. R.

APPLIED MEDICAL BACTERIOLOGY. By MAX S. MARSHALL, Ph.D., with the collaboration of HANET B. GUNNISON, M.A., ALFRED S. LAZARUS, Ph.D., ALIZABETH C. MORRISON, M.A., and MARIAN C. SHEVKY, A.B., Medical Center of the Univ. of California. Pp. 340; 8 ills. Phila.: Lea & Febiger, 1947. Price, \$4.50.

THIS book is a new approach to medical bacteriology. Although it is not a text in the usual sense, principles of bacteriology and procedures for the identification of microorganisms are skillfully combined as a laboratory manual. Thus the first 14 chapters are concerned with general bacteriologic procedures including such valuable chapters as those on general virus techniques, sanitation and biologic products. The final chapter constituting about half the book is devoted entirely to the laboratory diagnosis of commonly encountered infectious lesions or diseases. These are arranged alphabetically in order to facilitate reference. Under each disease are discussed the clinical aspects, the procurement of specimens, the character and identification of the causative organisms, and suitable methods of reporting laboratory findings to the clinical services. This book should be useful therefore not only for bacteriologists and pathologists, but also for practitioners of medicine in the proper procurement of specimens for bacteriologic examination.

R. N.

# PROTEINS AND AMINO ACIDS IN NUTRITION.

Edited by MELVILLE SAHYUN, M.A., Ph.D., Biochemist Consultant, Charles Godwin Jennings Hospital, Detroit. Pp. 566. New York: Reinhold, 1948. Price, \$7.50.

IN THIS cooperative effort, 18 authors have joined to prepare 13 chapters ranging from a historical review of the early literature upon protein nutrition to the protein nature of filtrable viruses. As the title implies, the authors confine themselves to various facets of our knowledge of proteins in nutrition. A partial listing of chapters will indicate the variety of information covered: "The Biological Utilization of Proteins and Protein Requirements"; "Caloric, Vitamin and Mineral Requirements with Particular Reference to Protein Nutrition"; "The Nutritive Aspects of Meat and Meat Products"; "The Relation of Hormones to Protein Metabolism"; "Plasma Proteins and Their Relation to Nutrition"; "Protein and Amino Acid Nutrition in Pediatrics and in Pregnancy"; "Protein Nutrition in Surgical Patients"; "Proteins as Related to Burns"; "Relation of Fluid and Mineral Balance to Protein Metabolism"; "The Protein Nature of Toxins, Antitoxins and Related Substances". In the appendix are included 2 tabulations of the proximate composition of American food materials and the nutritive values of 100 grams of selected foods, edible portions.

With this varied content it is evident that the biological significance of proteins and amino acids is being actively investigated. The answers to many of the questions raised are not yet available, but the discussions presented here should stimulate further investigations and increase our knowledge.

H. V.

# CONGENITAL MALFORMATIONS OF THE HEART.

By HELEN B. TAUSSIG, M.D., Assoc. Prof. of Pediatrics, Johns Hopkins Univ. School of Medicine. Pp. 618; 223 ills., 46 in color. New York: The Commonwealth Fund, 1947. Price, \$10.00.

THIS book is divided into 4 parts. The first (Chapters I through III), serving as an introduction deals with embryology, physiology and diagnostic methods. In Parts II and III (Chapters IV through XXV) the various congenital heart malformations are discussed. Finally, therapy is presented in Part IV (Chapters XXVI and XXVII).

Each chapter has been given the same care in organization and presentation as that reflected by the over-all plan of the book.

Clinical and pathological findings are amply illustrated with drawings of pathological specimens, with good reproductions of representative X-ray films, and in a few selected cases, with limb lead electrocardiograms. The anatomical alterations in the circulation produced by the various malformations are well shown by colored plates. Each chapter is concluded with a summary, a few illustrative cases, and several pertinent references to the literature.

In preparing this book Dr. Taussig has relied almost entirely upon her own experience to provide material. Many of the clinical observations and interpretations are her own, especially those based on fluoroscopic studies. She has made no attempt to survey the literature dealing with congenital heart disease or to list a complete bibliography.

Throughout the book Dr. Taussig emphasizes the importance of the clinical methods available to all physicians in the diagnosis of congenital heart malformations. This emphasis is justifiable as is the stress placed upon embryology, pathology, and physiology. There is, however, no specific discussion of the relative incidence of the various malformations, and much valuable information obtainable by angiocardiology and catheterization of the heart has been omitted. Passing mention is made of the diagnostic value of these procedures in certain malformations. Likewise no use has been made by the author of chest leads in the electrocardiographic studies.

This book is much needed and should prove useful to all physicians interested in congenital heart disease. It can be recommended without hesitation.

R. K.

# GYNECOLOGIC AND OBSTETRICAL UROLOGY. By

HOUSTON S. EVERETT, M.D., Assoc. Prof. of Gynecology, The Johns Hopkins Univ. 2d ed. Pp. 539; 232 ills. Balt.: Williams & Wilkins, 1947. Price, \$6.00.

WITH its emphasis on the very important relationship between diseases of the female genital system and the urinary tract, this book is a most valuable contribution, filling the gap commonly found in the literature and textbooks of these 2 specialties.

The field of urology, excluding only that which strictly pertains to the male, is completely covered by the author. The sections on anatomy, physiology and on renal function studies are excellently written, up to date, and beautifully illustrated, using many of the classic drawings of Max Brödel, as reproduced out of earlier texts originating from

the Johns Hopkins group. Diseases of the Female Urethra, Inflammations of the Bladder, Incontinence of Urine, Ureteral Obstructions, Pyelonephritis, Urinary Fistulas and The Management of Surgical Injuries to the Urinary Tract are ably presented, emphasizing etiology, diagnosis and management of these difficult problems in the female and bringing to the reader the summation of the work of many observers from a large clinic limited to urology in the female.

The new edition includes a section on the technique of indirect cystoscopy; a revision of the chapter on bladder neoplasms so as to include a summary of Jewett's recent work; the newer concepts of chemotherapy; and an increased number of illustrations and tables.

J. G.

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TELEPATHY AND MEDICAL PSYCHOLOGY. By JAN EHRENWALD, M.D., Associate in Psychiatry, Long Island College of Medicine. Pp. 212. New York: W. W. Norton, 1948. Price, \$3.00.

THE possibility of telepathic communication between individuals has frequently challenged the imaginative powers of the pseudo-scientific and lay writers, but the evidence presented has been mystic or poetic rather than objective and subject to critical scrutiny. Observations of the extreme sensitiveness of neurotic and psychotic patients to the attitudes of those around them do not readily lend themselves to re-examination under laboratory conditions; and on the other hand, the work of Dr. J. B. Rhine of Duke University with the so-called Zener cards provides data which are statistically assayable but provides little information as to the *modus operandi* of the phenomenon.

On this gap Dr. Ehrenwald focuses his interest. His association with "the Viennese school of Psychiatry" gave him, he feels, a psychoanalytic orientation and a lack of bias toward the schools of Freud, Adler, Jung and Stekel. Certainly he makes every effort to present an unprejudiced point of view. He contends that telepathic activity plays a more important rôle in the psychoanalytic situation than most therapists are willing to grant; and he adds the piquant comment that "no orthodox psychoanalyst appears to have ever come across patients dreaming in the 'Adlerian' jargon and . . . no strictly 'Adlerian' analyst has observed patients using the dream codex of the orthodox psychoanalyst . . . ." In spite of the serious considerations of telepathic phenomena in present-day psychoana-

lytic literature, there would appear to be some justification for the author's statement that these are regarded as "merely accidental" occurrences rather than as therapeutic tools of some potential value.

When considered from this point of view telepathy, in the author's opinion, may be expected to play a significant part in the formation of personality and the changes observed in the neuroses and psychoses. The concept is thought-provoking and the case-material (except, perhaps, in the chapter on Telepathy and Paranoia) offers strong supportive evidence. Whatever the reader's point of view, Dr. Ehrenwald's book is timely and stimulating.

E. B.

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#### THE SULFONAMIDES AND ALLIED COMPOUNDS.

By ELMORE H. NORTHEY, Ph.D., Administrative Director, Stamford Research Laboratories, American Chemical Monograph Series. Pp. 660; 323 tables. New York: Reinhold, 1948. Price, \$12.50.

SINCE the discovery of the antibacterial activity of the sulfonamides and related compounds, over 5000 new compounds have been synthesized. Much duplication of effort has gone into the preparation of these substances. Pertinent data upon their chemical and pharmacological properties are so scattered in the literature that it is all but impossible for the individual worker to attempt to correlate them. Accordingly Doctor Northey has compiled the information upon these compounds into tables in Beilstein order, listing melting points, antibacterial activities when known, and references to the literature. Many unpublished data are included, and journal references through December, 1944, are listed.

These data should be of great value as a research tool in the quest for new chemotherapeutic drugs. The book is not intended for a therapeutic guide, though it does contain much of interest to pharmacologists and clinicians. The methods of experimental evaluation of chemotherapeutic activity are summarized together with a tabulation of published data on the action of sulfa drugs against particular bacteria. The pharmacology of the more important compounds is presented in a separate chapter. The various theories advanced to explain the mechanism of action of the sulfonamide drugs are also reviewed. In a final chapter Doctor B. W. Carey presents an adequate summary of the clinical evaluation of the sulfonamide drugs.

H. V.

## NEW BOOKS

*Medical Clinics of North America.* January, 1948. Chicago Number. "Symposium on Endocrinology." Pp. 1-299. Phila.: W. B. Saunders. Price, \$16.00 a year.

THIS number is composed of 11 articles under the Editorship of Dr. Willard O. Thompson, and, in addition, 11 Clinics on other subjects. The Symposium on Endocrinology discusses in practical detail such problems as sterility in the male and female, hypogonadism in the male, uterine bleeding, testosterone treatment of breast cancer, problems of growth and the treatment of Graves' disease with radioactive iodine. The articles, by authors who are recognized authorities in their fields, present a thoughtful analysis of the problems involved. The Clinics on other subjects are diverse, ranging from an excellent discussion of the detection of food allergy to a review of precordial leads in electrocardiography. The volume may be recommended for these practical yet stimulating articles.

F. D.

## NEW EDITIONS

*Illustrative Electrocardiography.* By JULIUS BUBSTEIN, A.B., M.D., Chief of the Cardiac Clinic, Morrisania City Hospital, New York, and NATHAN BLOOM, M.D., F.A.C.P., Assoc. Prof. of Medicine, Medical College of Virginia. 3rd ed. Pp. 325; 99 plates. New York: D. Appleton-Century, 1948. Price, \$6.00.

THIS edition is rewritten and includes, very briefly, the newer techniques of electrocardiographic examination. The text contains few theoretical considerations, and no controversial material. The illustrations are well chosen. Chapters on the phonocardiogram and radiology of the heart have been added. There is no bibliography, but a subject index is appended. The book is distinctly one for the beginner, and, as such, will serve a useful purpose.

J. V.

*Laboratory Technique in Biology and Medicine.* By E. V. COWDERY, Prof. of Anatomy, Washington Univ. 2d ed. Pp. 269. Balt.: Williams & Wilkins, 1948. Price, \$4.00.

EXCEPT for a few introductory pages on Choice of Method and Standardization of Stains, the text consists of techniques (histological, physiological, biophysical and biochemical) conveniently arranged in alphabetical order. This edition "has expanded the subject matter to include re-

lated physical methods, and microchemical and other laboratory techniques. . . . Also included are new methods developed since the publication of the first edition, and improvements in standard techniques."

*Laboratory Experiments in Physiology.* By W. D. ZOETHOUT, Ph.D., Prof. Emeritus of Physiology, Chicago College of Dental Surgery. 4th ed. Pp. 263; 97 figs. St. Louis: C. V. Mosby, 1948. Price, \$3.00.

"THE book is designed to serve as a useful guide for courses ranging from elementary human physiology to advanced mammalian or medical physiology."

*Source Book of Orthopaedics.* By EDGAR M. BICK, M.D., F.A.C.S., Assoc. Orthopedic Surgeon, Mt. Sinai Hospital, New York. 2d ed. Pp. 540; 31 ills. Balt.: Williams & Wilkins, 1948. Price, \$8.00.

*Psychobiology and Psychiatry.* By WENDELL MUNCIE, M.D., Assoc. Prof. of Psychiatry, Johns Hopkins Univ. 2d ed. Pp. 620; 70 ills. St. Louis: C. V. Mosby, 1948. Price, \$9.00.

*Clinical Toxicology.* By CLINTON H. THIENES, M.D., Ph. D., Prof. of Pharmacology, Univ. of Southern California, and THOMAS J. HALEY, Ph. D. 2d ed. Pp. 373; illustrated. Phila.: Lea & Febiger, 1948. Price, \$4.75.

SINCE the 1st edition appeared 8 years ago (See AM. J. MED. SCI., 199, 726, 1940) the text has been so greatly enlarged and revised that the book has been completely reset. It is divided into 9 sections, Convulsant Poisons, Central Nervous System Depressants, Peripherally Acting Nerve Poisons, Muscle Poisons, Protoplasmic Poisons, Poisons of the Blood and Hematopoietic Organs, Principles of Treatment, An Outline of Symptom Diagnosis, Chemical Diagnosis of Poisoning. It should be of value to the general practitioner and to specialists in many fields.

*Thrombangioma obliterans des Gehirns.* By J. LLAVERO. Pp. 248; 15 ills. Basle, Switzerland: Benno Schwabe, 1948. (Imported by Grune & Stratton.) Price, Geb. Fr. 24.

*Über die Kaliumbestimmung in Biologischer Substanz.* Von W. W. RIEBEN, Professor der Medizin. Pp. 73; 4 ills. Basle, Switzerland: Benno Schwabe, 1947. (Imported by Grune & Stratton.) Price, Geb. Fr. 12.

*You Can Be Thin! Slenderness Through Psychology.* By HERMAN FRIEDEL, M.D. Pp. 117. New York: Caxton House, 1948. Price, \$2.00.

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

AUGUST, 1948

## ORIGINAL ARTICLES

### AN EVALUATION OF VARIOUS EXAMINATIONS PERFORMED ON SEROUS FLUIDS\*

By SPENCER K. PHILLIPS, M. D.,  
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AND

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SECTION ON SURGICAL PATHOLOGY, MAYO CLINIC  
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For many years it has been possible to make a diagnosis of the disease underlying abnormal collections of fluid in the serous cavities in certain cases. However, many times serous effusions occur and it is impossible to make more than an unsatisfactory, indefinite diagnosis in the absence of convincing evidence pointing in one direction. It was with the hope of adding to the knowledge which might be derived from the examination of serous fluids that this study was undertaken, even though the evidence so derived could hardly be more than presumptive.

**Review of the Literature:** The first report located in which anyone found malignant cells anywhere other than in tissues was by Beale,<sup>2</sup> who recognized a clump of malignant cells in the sputum of a patient who had carcinoma of the pharynx. Later other clinicians

<sup>9,44,45</sup> found malignant cells by examining stained smears of pleural and ascitic fluid. Bahrenberg<sup>1</sup> described a technic for embedding the sediments from centrifuged fluids and sectioning them for examination. In 1900, Mandelbaum<sup>30</sup> was able to diagnose actinomycosis by fixing pus in formalin, embedding it in celloidin and demonstrating the *Actinomyces* microscopically. Steiner<sup>50</sup> used the technic described by Mandelbaum to demonstrate malignant cells in effusions. This technic with minor variations still is used by some but it has been supplanted <sup>6,10,29,32,49,51,54,58</sup> in most cases by a different technic in which the specimen is embedded in paraffin for section as described by the same author<sup>31</sup> at a later date. A method of making frozen sections of the sediment fixed in formalin without the use of paraffin was described by Venable<sup>54</sup>;

\*Abridgment of thesis submitted by Dr. Phillips to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.



by this method he was able to obtain good material for examination. Some authors<sup>11,36</sup> have stressed that paraffin sections are greatly superior to stained smears in examining sediments of serous effusions, but the results of those<sup>28</sup> who used smears seem to compare favorably with the results of those who used sections.

The presence of mitotic figures in the cells of effusions has been discussed by many writers, but there has been considerable disagreement as to the amount of dependence which may be placed on the finding of them in diagnosis. It has been reported<sup>20,57</sup> that mitotic figures have been found in the benign cells of effusions, but many authors<sup>12,15,16,28,36,55</sup> consider them presumptive evidence of malignancy. Evidence of atypical mitosis generally has been found only in malignant cells.<sup>12,58</sup>

It is generally agreed that the observation of indefinite clumping of the cells or formation of sheets is of little if any value in diagnosis of malignant disease,<sup>12,13,28</sup> but that the finding of definite organoid arrangement of the cells, such as the formation of acini, contributes positive evidence and makes a high degree of accuracy in diagnosis possible.<sup>11-13,15,16,19,25,56</sup> Some<sup>30,45</sup> have said that the diagnosis can be made when such formations are found but the absence of the organoid arrangement does not necessarily rule out the presence of the disease.

Multinucleation and formation of giant cells have been discussed by several authors,<sup>12,13,15,16,35,55</sup> but none considered them of great importance except when the giant cells are of the tumor type.

Nearly all of the writers on the subject have recognized some finer differences between the individual characteristics of the malignant cell and those of the normal cell and attached more or less importance to these dif-

ferences in diagnosis. Large, deep-staining cells with large nuclei have been considered as suggestive of malignancy,<sup>12,13,28,58</sup> and some authors<sup>12,17,20-28,38,42,43,57</sup> have stressed the importance of an increase in the relative size of the nucleolus as compared with that of the nucleus. Many<sup>12,28,49</sup> have warned against designating as malignant the highly atypical cells found in fluids which have been present a long time while others<sup>13,58</sup> have considered eccentricity of the nucleus to be of diagnostic assistance.

All writers have emphasized that diagnosis of malignant disease based on examination of serous effusions carries a high degree of accuracy, but negative findings are of less importance. Nearly all report<sup>3,19,36,49,58</sup> that the diagnosis of malignant disease was made correctly on the basis of this examination in from 50 to 80% of their cases. In from 3 to 5% the results were erroneously positive.

Most investigators<sup>3,34,41</sup> of the subject have reported that the finding of various blood elements in serous effusions is of little aid in diagnosis. Norris and Landis<sup>49</sup> believed that a predominance of lymphocytes in pleural effusions is very suggestive of tuberculosis. Several<sup>3,39,52</sup> have concluded that neoplasms and tuberculosis are the commonest causes of hemorrhagic pleural effusions.

Although exudates, such as the effusions caused by inflammatory and neoplastic processes, tend to have higher specific gravity and concentration of protein than do transudates, chemical studies of serous exudates have not been found useful in making a diagnosis except in rare instances.  
4,5,7,11,13,14,19,53

Moore and Van Slyke<sup>37</sup> demonstrated that the specific gravity of the blood plasma parallels the concentration of protein in the plasma with sufficient exactness to indicate the con-

centration of the latter. The maximal deviation in their cases was 0.6 gm. per 100 cc. of plasma. A variation on their formula was found by Weech and his associates<sup>56</sup> to be accurate in working with transudates in dogs, and by Paddock<sup>40</sup> to apply in serous effusions from human beings. The formula is: grams of protein per 100 cc. of plasma =  $353.1 (G - 1.00759) \pm 0.058$ .  $G$  represents the specific gravity at 20° C.

**Materials and methods:** For this study 103 specimens of fluid from ninety-two consecutive patients with ascites, pleural effusion or pericardial effusion who underwent paracentesis, thoracentesis, pericardial aspiration, peritoneoscopy or laparotomy were collected and studied. The gross appearance of the fluid was noted and the specific gravity was determined with the ordinary laboratory hydrometer as soon as the fluid was obtained.

At first erythrocyte and leukocyte counts were attempted, but because so many of the specimens were grossly contaminated by blood in the operating room and because many of the cells had settled before time was available for the study, thus making results inaccurate, these determinations had to be abandoned before they were made on all fluids and are not reported. However, remarks as to the relative cellularity of the fluids, estimated from the appearance of the slides, were recorded throughout.

Specimens were centrifuged at 1,800 to 2,000 rpm for 15 minutes and the sediments obtained were smeared on slides and dried in the air at room temperature. Some of each set of slides were then fixed in 10% solution of formalin for 12 to 24 hours, stained with hematoxylin and eosin, and mounted with cover slips in Canada balsam. Other smears were stained by hematologists with Wright and Giemsa stains in their usual manner for preparing blood smears.

A differential count of lymphocytes, polymorphonuclear leukocytes and monocytes was made. The number of mesothelial cells, including malignant cells in this class when they were present, was noted for each 100 leukocytes.

Smears of each specimen were examined carefully for the presence of abnormal cells, often with the oil immersion lens when its use was needed to examine the nuclear detail closely.

Clinical pathologists assisted by determining the total concentration of protein, nonprotein nitrogen and chloride in the fluid.

In most instances cultures for bacteria were obtained. In many instances guinea pigs were inoculated with some of the fluid and subsequently necropsy was performed in the Section on Bacteriology.

Finally, the histories for all the patients were checked to discover the diagnoses and, as far as possible, to determine the subsequent course of the disease. As more than five years had elapsed since the beginning of the study, this was often of much interest.

**Observations:** Fifty-three specimens of fluid were obtained in 46 cases in which a diagnosis of malignant disease had been made clinically, on roentgenologic examination, biopsy or necropsy, but in only 34 cases in which 40 specimens were obtained, was there any evidence that the tumor might have involved the serous surfaces. In 19 (20 specimens) of the 34 cases a positive diagnosis of malignant disease could be made on the basis of the finding of malignant cells in the fluids. All fluids in which findings were doubtful were classified as negative for malignant disease.

Four specimens of fluid were obtained in the same number of cases in which a diagnosis of possible malignant diseases had been made. No positive results were found on examination of the smears.

Among the 46 specimens from 42 patients who did not have malignant disease, one was considered to contain malignant cells.

A summary of the characteristics found on examination of the smears may be found in Table 1. Consideration was given chiefly to the finer cytologic characteristics of the individual cells, such as the presence of mitotic figures, large, deep-staining nuclei and large, prominent nucleoli. Smears stained with Wright or Giemsa stain were often useful because of the greater demonstration of nuclear

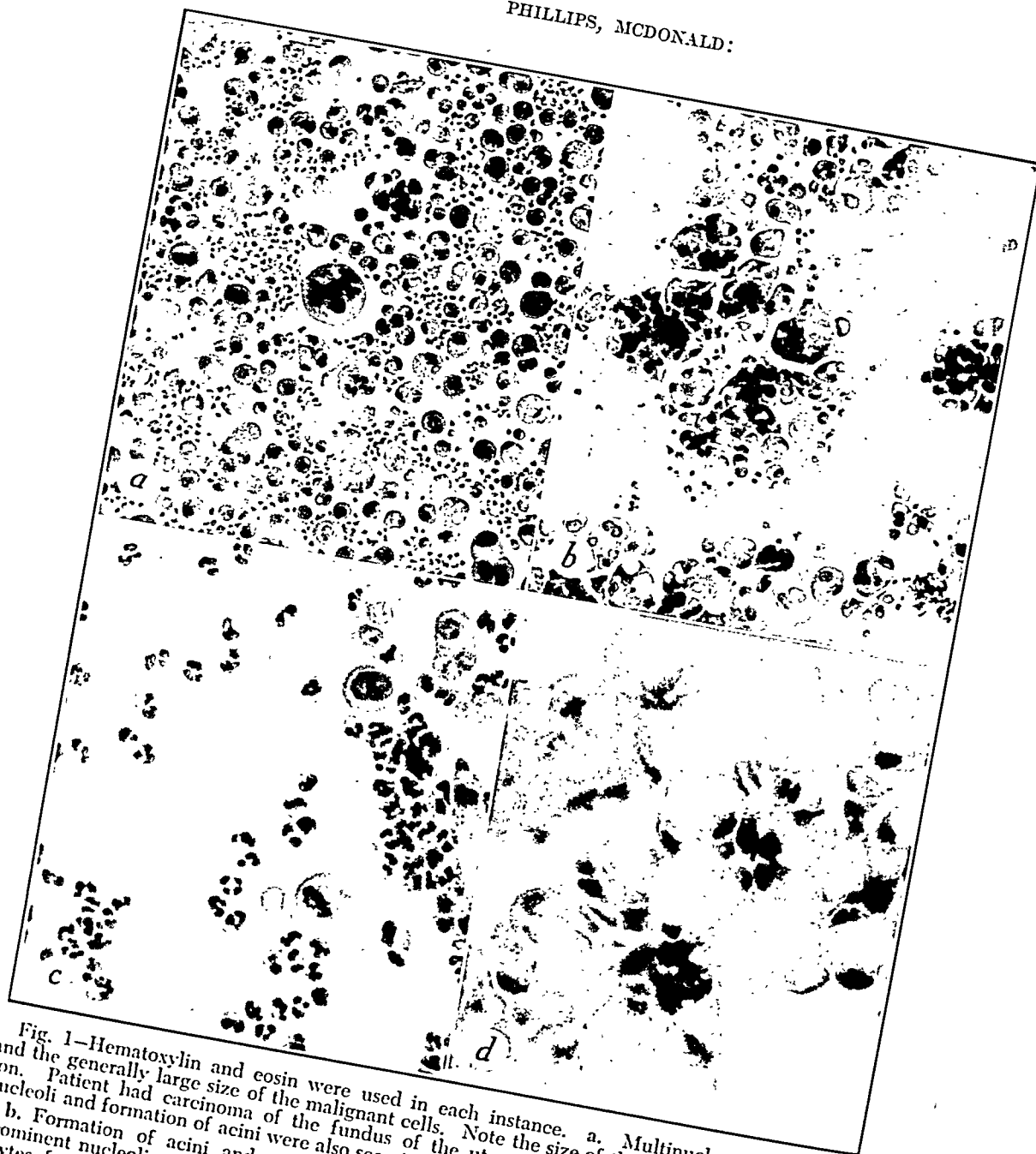


Fig. 1—Hematoxylin and eosin were used in each instance. a. Multinucleated giant cells and the generally large size of the malignant cells. Note the size of the leukocytes for comparison. Patient had carcinoma of the fundus of the uterus. Mitotic figures, large, prominent nucleoli and formation of acini were also seen in the smear. (x125.)  
 b. Formation of acini and signet-ring cells. Mitotic figures, multinucleated cells, large, prominent nucleoli, and acini are seen in other parts of the slide. Note the size of the lymphocytes for comparison. The peritoneum of the patient was studded with implants from a grade 4 (Broders' method) adenocarcinoma of the ovary. (x125.)  
 c. The metaphase of mitosis, multinucleation and a fairly large, prominent nucleolus. Note the size of the leukocytes for comparison. The smear also showed eccentric nuclei and irregular clumping of cells, but no organoid arrangement. The patient, 12 years old, had juvenile cirrhosis and was alive and well at least 4 years after this slide was made (x400).  
 d. Signet-ring cells in acini with a mitotic figure in anaphase. Note the size of the lymphocyte for comparison. The patient had implants of adenocarcinoma, grade 4, throughout the pelvic peritoneum as found on peritonoscopy. (x400.)

detail than is afforded by hematoxylin and eosin. The presence of definite organoid arrangement of cells, such as in acini, was found to be a very useful diagnostic aid; no errors were made in this series when the presence of these cells was used as a criterion for the diagnosis of malignancy. The finding of eccentricity of the nucleus, formation of signet-ring cells, multinucleation and irregular clumping of the cells was not useful; they were found to occur frequently in fluid from patients without malignant disease. The erroneous diagnosis of malignancy was made on the basis of the finding of several mitotic figures in fluid which also showed eccentric nuclei, clumping and multinucleation. The pa-

tient was a boy with juvenile cirrhosis. He was alive and well at least 4 years later.

Fig. 1 shows some of the cellular characteristics mentioned.

**Specific Gravity.**—In fluid containing malignant cells the specific gravity ranged from 1.011 to 1.027, with an average of 1.022. In cases of malignant disease in which malignant cells were not found in the fluid the range was 1.012 to 1.030, the average being 1.020. In cases of nephritis the range was 1.006 to 1.012, with an average of 1.010. The range in cases of cirrhosis was 1.008 to 1.020; the average, 1.013. The specific gravity of the fluid in two cases of cardiac decompensation was 1.018 and 1.020. In the mis-

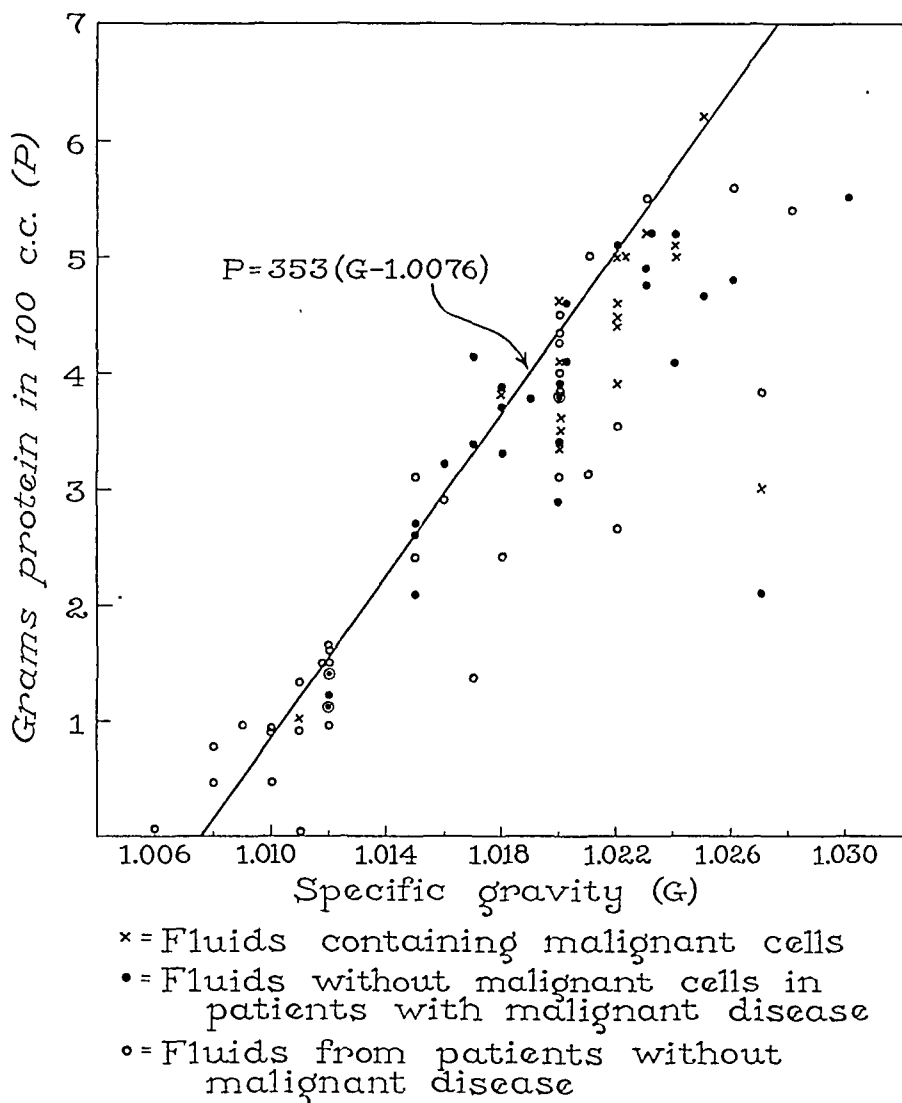


Fig. 2. Concentration of protein calculated by means of the formula of Weech and his colleagues.<sup>28</sup>

cellaneous group in which the conditions were chiefly inflammatory, the range was 1.015 to 1.028; the average, 1.020. The only tuberculous effusion in the series had a specific gravity of 1.026.

The formula of Weech and his associates was used to calculate the concentration of protein in the fluids from the specific gravity,<sup>18,46</sup> and the results are represented graphically in Fig. 2. It may be seen that the values deviate considerably from the straight line represented by their formula and that the scatter is greatest for the fluids with high concentration of protein and specific gravity. The amount of variation, however, has no relationship with the disease causing the formation of fluid. It may be seen further that there is so much spread of the values for protein in the fluids in cases of any type of disease that this factor is of no use in making a diagnosis in any individual case.

It was noted that fluid containing malignant cells tended to have a larger amount of sediment than others, but to a degree which could be considered as suggestive only in extreme cases. Except in purulent fluids, most of the fluid, regardless of the disease present, had a predominance of lymphocytes over polymorphonuclear leukocytes. Exceptions to this tendency occurred irregularly in all types of cases. A high number of mesothelial cells in relation to the number of leukocytes was ordinarily found when malignant cells were present, but sometimes a high number was found when malignant cells were not present.

Concentrations of nonprotein nitrogen and chloride in fluid varied over a considerable range without relation to the disease present. Correlations with those in the blood were unavailable for this study.

**Comment.** An attempt should be made to account for the presence of serous effusions in cases of malignant disease in which the diagnosis cannot be confirmed by examination of the fluid. Malignant cells will be found in the fluid only if the malignant process involves the serous surface. Under

this circumstance cells and groups of cells may break off and float free in the fluid, and the surface may become seeded with daughter tumors if some of these cells are able to become implanted and grow.<sup>8</sup> If the number of free-floating cells is small they may not be found in the material examined because of their scarcity.

On the other hand, fluid may be formed in malignant disease in which the serous surface is not involved by the tumor. The inflammatory reaction about a carcinoma of the colon, for example, might be sufficient to cause ascites to form, even though the tumor cells had not penetrated the serosa. Malignant tumors of the ovary might well cause ascites through the same, poorly understood mechanism as do fibromas in Meigs's syndrome.<sup>33,47</sup> Metastasis to the liver through venous channels may cause venous obstruction in the liver and ascites through the same mechanism as cirrhosis. Ascites could be caused by blockage of the lymphatic channels in the regional lymph nodes by metastasis, but the ascitic fluid then should be chylous and it seldom is in actual practice.

Lymphatic obstruction could cause pleural effusion without serosal involvement, and the fluid would not necessarily be chylous unless the thoracic duct were impinged upon. Here again, the effusion might result from ovarian tumors, as in Meigs's syndrome.<sup>33,47</sup> Fluids may collect in cases of inflammatory conditions also without serosal involvement, especially if bronchial obstruction is present.

**Summary.** The diagnosis of malignant disease was made by study of the characteristics of individual cells as seen in stained smears of the sediment obtained by centrifuging serous effusions in 19 of our 46 cases of malignant disease in which the fluid was examined. Absence of the charac-

teristic cell did not rule out the diagnosis. The use of Wright and Giemsa stains for the smears in addition to hematoxylin and eosin was found to be of some assistance in some cases because they revealed the intranuclear detail more clearly. The value of bacteriologic studies on pleural and ascitic fluids was not questioned or investigated in this study.

In general the fluid which might be considered to be an exudate had higher specific gravity than the transudates, but the values overlapped considerably. Specific gravity correlated fairly closely with the concentration of the protein in the fluid in most cases, but the correlation was not as close as had been reported by others. Knowledge of the specific gravity of a serous fluid was probably of as much value diagnostically as that of the protein content.

A large cell pack suggested the presence of malignant disease with involvement of the serous surface, but a small cell pack was of no significance in diagnosis.

Knowledge of the nonprotein nitro-

gen and chloride was of no value in determining the cause of serous effusions.

Differential counts were too variable to be of diagnostic value.

Malignant disease can cause the formation of serous effusions without involvement of the serous surface by tumor cells.

TABLE 1  
CELLULAR CHARACTERISTICS OF  
THE FLUID

	Malignant disease	Possible malignant disease	Non-malignant disease
Case	Specimens		
Cases . . . . .	46	4	42
Specimens . . . . .	53	4	46
Malignant cells in contact with serosa . . . .	34	40	0
Diagnosis of malignant disease made on basis of fluid examination	19	20	0
Mitotic figures . . .	11	11	0
Large, prominent nucleoli . . . . .	22	24	0
Eccentric nuclei	17	17	2
Signet-ring cells	25	27	1
Clumping of cells	12	12	2
Formed acini . . .	10	11	0
Multinucleated cells . . . . .	28	29	4

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# THE USE OF RADIOACTIVE IODINE IN THE DIAGNOSIS OF THYROID DISEASE

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Radioactive iodine when administered by mouth or by vein is concentrated selectively by thyroid tissue.<sup>1</sup> The use of the Geiger-Muller tube after the administration of radioiodine for localization of functional thyroid tissue, indigenous or metastatic, has become a generally accepted procedure. When metastases are present at a distance from the neck, simple detection of the focus of radioactivity

only when the source is located within a relatively small angle in front of the tube. We have used this device in order to obtain a graphic representation of the distribution of thyroid tissue. When correlated with physical examination, this method permits greater accuracy in diagnosis. Sixty patients with a variety of affections of the thyroid were studied. In this report results with representative types

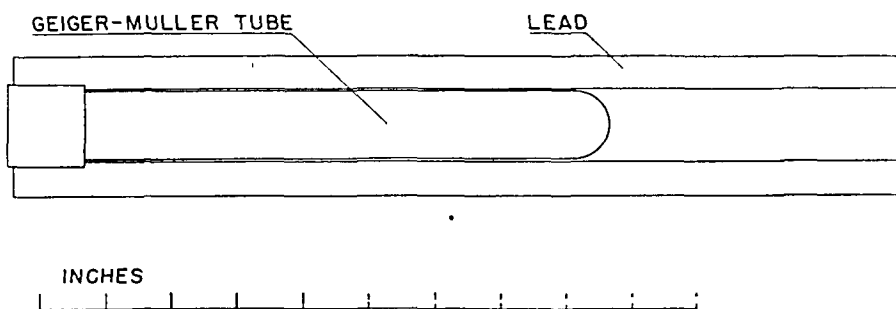


Fig. 1.—Diagram of the collimated Geiger-Muller tube.

has been sufficient for the conclusion that functional thyroid cancer is present. When it is necessary to obtain information about the distribution of thyroid tissue in or near the gland itself, a more exact technique is required. The ordinary Geiger-Muller tube has a large acceptance angle. Marinelli<sup>2</sup> has introduced a collimated Geiger-Muller tube (enclosed in a lead tube) which responds to radiation

of diseases are presented.

Studies were made 1 to 2 days after the oral administration of  $I^{131}$ . Measurements were done with a Sylvania gamma counting Geiger-Muller tube enclosed in an open ended lead tube of 1" inner diameter made with a  $\frac{1}{2}$ " wall thickness (Fig. 1). The whole assembly was supported on a portable X-ray tube stand. The "resolving power" of the collimating tube was



checked with two caps,  $\frac{3}{4}$ " in diameter, containing the same amount of  $I^{131}$ . There was a distinct dip in the profile when the centers of the caps were 1" apart.

The tube was first approximated to the skin at the level of the thyroid isthmus in the midline and the number of counts per second determined for a period of about 60 seconds (128 to 4096 counts). The tube was then moved laterally and measurements made at  $\frac{1}{2}$ " intervals without changing the level of the tube. Counts per second were plotted against distance from midline. We will refer to these graphs as "horizontal profiles."

53 year old Puerto Rican woman was admitted to the hospital with a 10 month history of swelling of the neck, dyspnea, palpitation, 60 pound weight loss, nervousness, and sweating. Physical examination revealed a thin nervous female with a diffusely and symmetrically enlarged thyroid estimated to weigh about 100 grams. The basal metabolic rate was plus 64%. After administration of 0.1 mc. of  $I^{131}$ , a horizontal profile was determined (Fig. 2).

The profile is symmetrical. This has been seen in hyperplastic thyroids and in normals. The apex of the triangle is occasionally flattened and broadened when the lateral lobes are greatly enlarged.

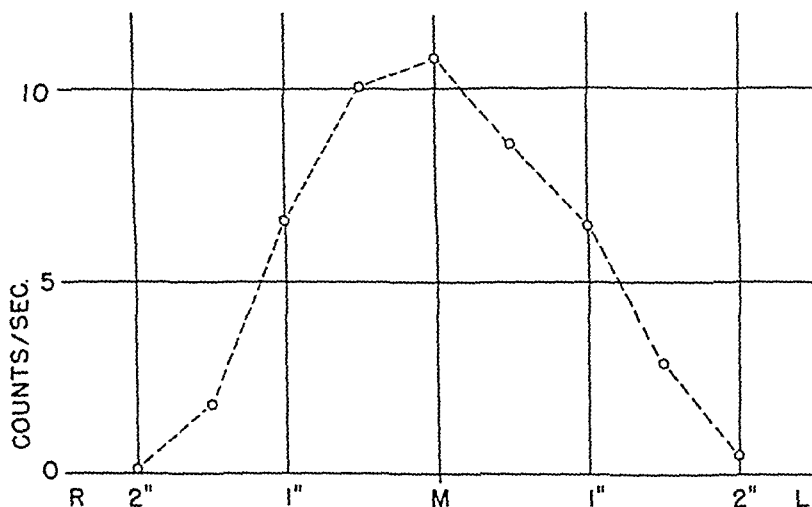


Fig. 2.—Horizontal profile in Case 1, diffuse thyroid hyperplasia.

"Vertical profiles" were obtained in a similar way. The tube was moved along the midline or parallel to it, and the counts per second were plotted against distance from the vertex of the skull (in inches). In taking the vertical profiles, the tube was approximated to the skin in each position. In addition to these studies, surveys of the limbs and pelvis for metastases were made routinely but were not plotted.

Typical curves in 7 representative cases are presented below, with brief clinical abstracts.

Case 1: J.F. Diffuse toxic goiter. This

Case 2: I.M. Aberrant lingual thyroid. This 20 year old girl was admitted with a chief complaint of difficulty in swallowing. Eight years prior to admission similar dysphagia had caused her admission to another hospital where a growth at the base of the tongue was excised. Five years prior to admission, the symptoms, which had been relieved, began to recur and increased in severity until admission. There were no symptoms suggesting hyperthyroidism. Physical examination revealed a red, firm, nontender mass 1" in diameter at the base of the tongue in the region of the foramen caecum. The thyroid was not palpable in the neck. The basal metabolic rate was plus 3%. X-ray

of the chest was normal. After administration of 0.5 mc. of  $I^{131}$  a vertical mid-line profile was determined (Fig. 3). The horizontal profile was symmetrical as in Case 1.

The apex of this profile is at the level of the tongue (9" below the vertex), as compared to a normal profile, with the apex at the level of the cricoid (12" below the vertex). This demonstrates the presence of functioning thyroid tissue at the level of the

tongue. The absence of an increase of counts at the level of the neck shows the absence of a functional thyroid gland in the usual position. The pre-operative diagnosis of aberrant lingual thyroid gland was made; in the absence of a normal thyroid, operation was not advised. Biopsy showed lingual mucosa with subjacent thyroid tissue, microscopically and on autoradiographs.

Case 3: D.T. Nontoxic thyroid adeno-

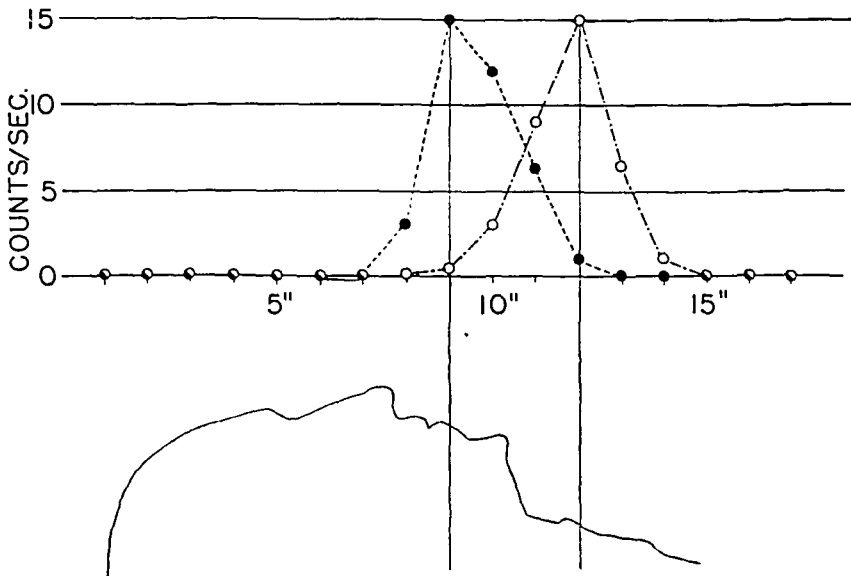


Fig. 3.—Vertical profile in Case 2, lingual thyroid. Solid circles are the record of the patient. The open circles are the profile of a normal patient.

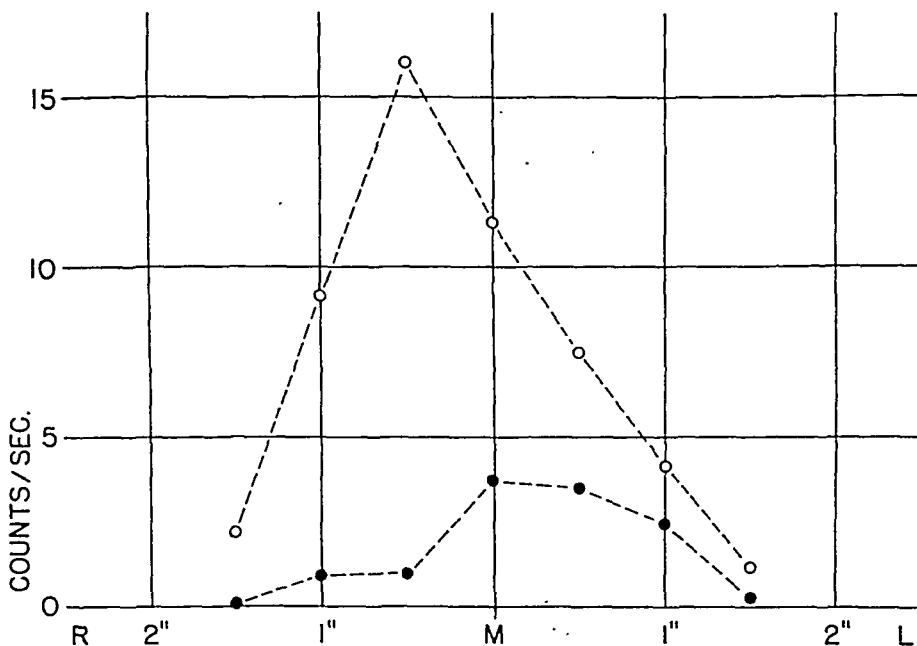


Fig. 4.—Horizontal profile in Case 3, nontoxic thyroid adenoma of the right lobe. The open circles are the preoperative profile; the closed, the postoperative.

ma. This 25 year old female was admitted with 4 month history of gradual swelling of the neck. There was no pain. There were no symptoms of thyroid toxicity. Physical examination showed no abnormality other than a palpable nodule, plum sized, in the right lobe of the thyroid gland. The basal metabolic rate was plus 1%. The patient received 0.5 mc. of  $I^{131}$  and a horizontal profile was determined (Fig. 4). The mass was resected by subtotal right hemithyroidectomy and the diagnosis confirmed.

The preoperative profile shows the maximum radiation  $\frac{1}{2}$ " to the right of the midline. The area under the curve to the right of the midline is notice-

soft above and firm below. This mass moved with swallowing and was not fixed to the skin or underlying tissue. The basal metabolic rate was plus 3%. After administration of 0.4 mc. of  $I^{131}$ , a horizontal profile was recorded (Fig. 5). The preoperative clinical diagnosis was thyroid adenoma or carcinoma; it was surmised that hemorrhage might be responsible for the sudden pain and swelling. At operation, hemorrhage into a colloid cyst was found. The lesion was removed. There was no evidence of malignancy.

The profile shows maximum radiation  $\frac{1}{2}$  to 1" to the left of the midline on the side opposite to the palpable

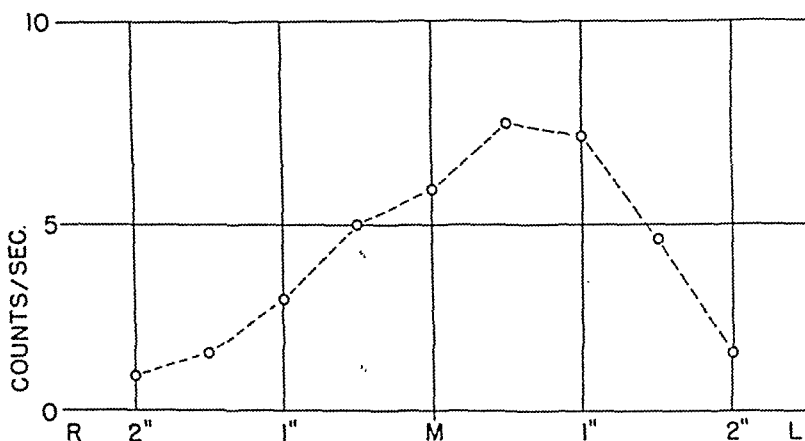


Fig. 5.—Horizontal profile in Case 4, colloid cyst of the right lobe of the thyroid.

ably greater than that on the left; this corresponds to the physical findings. Postoperative profile showed the removal of most of the right lobe; almost all the uptake on that side had disappeared.

Case 4: B.C. Colloid cyst of the thyroid. This 65 year old female presented herself with a two week history of pain in the right side of the neck. The pain had appeared suddenly on awakening and had maintained an aching character for most of the subsequent period. The patient observed a mass develop in the right side of the neck. There were no symptoms of hyperthyroidism or of hypothyroidism. There was no recent weight loss or loss of appetite. In the right side of the neck there was a peach-sized mass which was

mass. This suggests, in contrast to Case 3, that the mass was not composed of functioning thyroid tissue. Similar findings have been observed in other cases of colloid cyst and also in cases of anaplastic carcinoma.

Case 5: M.S. Aberrant thyroid. This 26 year old woman had noted gradual swelling of the right side of the neck for three months prior to admission. There were no metabolic disturbances. At another hospital tissue was obtained by aspiration and was reported as papillary carcinoma of the thyroid. Physical examination revealed a smooth, freely movable thyroid gland of approximately normal size. In the right cervical region, under the sternomastoid muscle, there were two firm masses each about 1" in diameter.

No other nodes were palpable. The basal metabolic rate was minus 9%. 0.5 mc. of  $I^{131}$  was administered and a horizontal profile recorded (Fig. 6). Studies over the remainder of the body revealed no radioactive foci. A right radical neck dissection was performed with right hemithyroidectomy and subtotal left hemithyroidectomy. Three retrosternomastoid nodes replaced by aberrant papillary adenoma of the thyroid were reported. The thyroid tissue was not abnormal. Radioautograph of the nodes showed uptake of  $I^{131}$ .

The preoperative profile shows a marked maximum to the right of the midline. In view of the antecedent biopsy this was considered indicative of metabolically functional carcinoma. The postoperative profile is consistent

with complete removal of functional tissue from the right side of the neck. Similar curves have been found in cases of functional unilateral carcinoma. It is planned to repeat the profile at intervals of 3 months to detect any recurrent growth of thyroid tissue on the left.

**Case 6:** E.C. Recurrent carcinoma of the thyroid. This 37 year old male was well until 1940 when a painless lump in the right side of the neck developed. This was biopsied; radiotherapy given for the next three years. The pathologic report is not available. In 1943 a right radical neck dissection was performed. Papillary carcinoma of the thyroid was found. Recurrent masses were resected in 1944 and in 1945. Typical diabetes mellitus developed in 1947. Within the

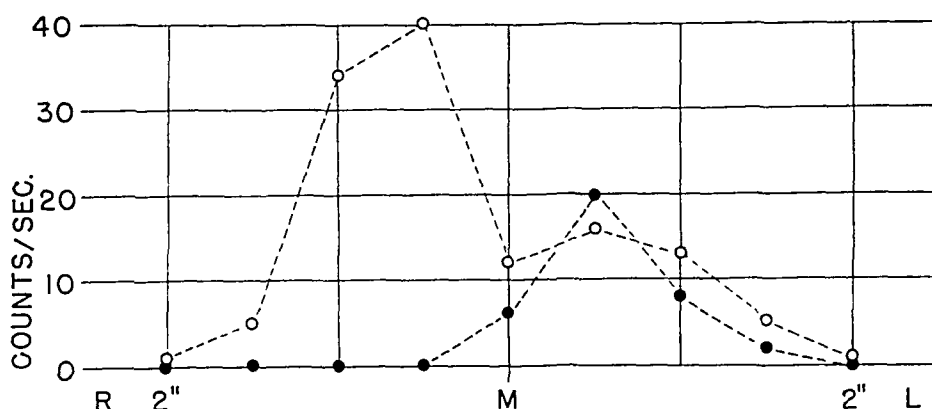


Fig. 6.—Horizontal profile in Case 5, lateral aberrant thyroid. The open circles are the preoperative profile; the closed, the postoperative.

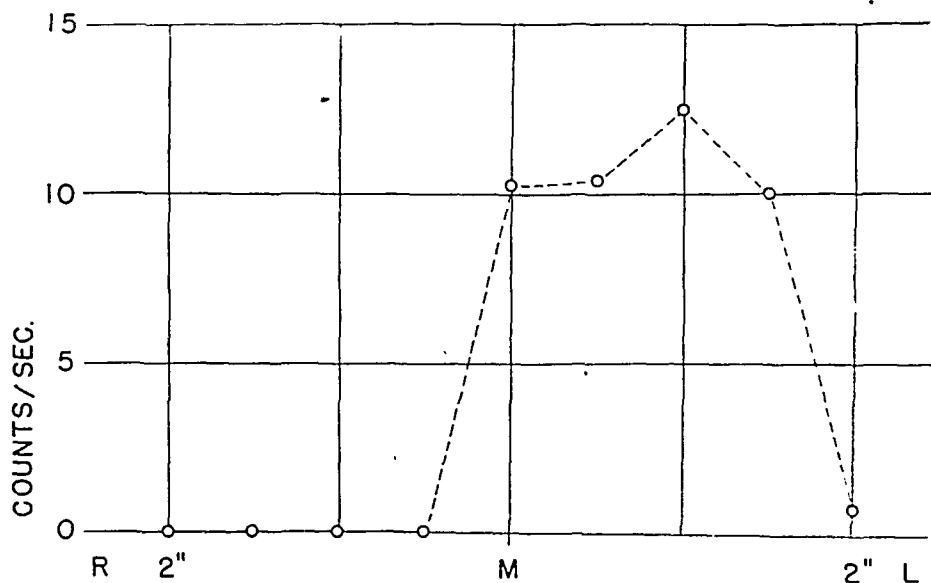


Fig. 7.—Horizontal profile in Case 6, papillary carcinoma of the thyroid with recurrence after right radical neck dissection.

few weeks prior to admission the patient noted the onset of dyspnea and productive cough. Considerable swelling developed at the right side of the neck. Physical examination revealed stony nodular masses 1" to 2" in diameter fixed to the deeper structures of the neck bilaterally. The right upper lobe of the lung presented signs of atelectasis. Roentgen examination confirmed this impression and bronchoscopy revealed metastatic thyroid tissue occluding the bronchus. The liver was palpable 3 fingers below the costal margin and was very nodular. After the administration of 3.0 mc. of  $I^{131}$ , profile studies were done (Fig. 7). The patient left the hospital against advice without further treatment or study.

The profile showed no measurable uptake of iodine on the operated right side; the curve is characteristic of unilateral radical dissection of the neck.

This finding despite the palpable masses on this side led to the conclusion that the tumor was devoid of metabolic activity. Measurements over the chest and liver were at background level and supported this conclusion.

Case 7: A.F. Metastatic carcinoma of the thyroid. This 60 year old German born woman presented herself in May 1947 with known goiter of at least 30 years' duration. There were no toxic symptoms but local pressure had recently increased. The thyroid was nodular. The basal metabolic rate was plus 19%. Subtotal thyroidectomy was performed and primary adenocarcinoma was discovered in one of the goitrous nodules. Three months postoperatively, a mass, 1 inch in diameter, developed at the insertion of the right sternomastoid muscles behind the clavicle. Roentgen films of the chest revealed 3 large pulmonary infiltrations considered

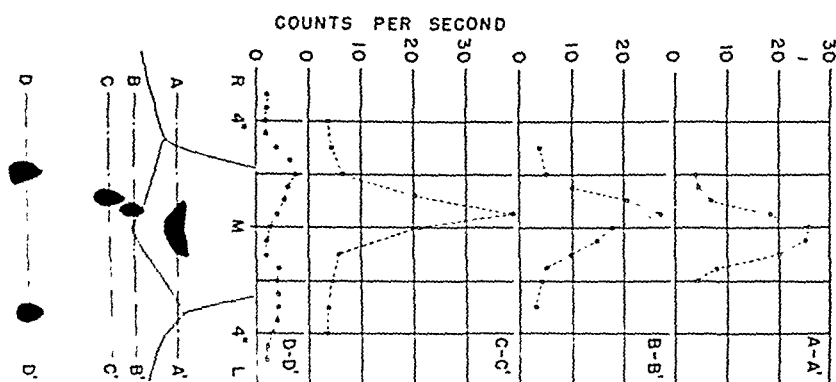


Fig. 8.—Horizontal profiles at various levels in Case 7, adenocarcinoma of the thyroid. The diagram represents the location of nodular metastases as demonstrated by Roentgen-ray.

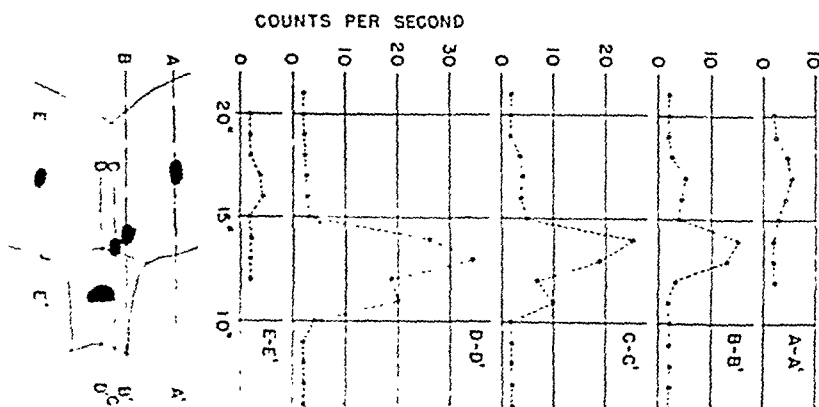


Fig. 9.—Vertical profiles in various planes, Case 7.

indicative of metastatic tumor. The patient remained asymptomatic. She was referred to this department where 3.0 mc of  $I^{131}$  was administered. Horizontal and vertical profiles were recorded (Figs. 8,9). Since the tumor exhibits distinct metabolic activity, for the metastases take up iodine, treatment has been instituted with repeated doses of 50 mc. of  $I^{131}$ .

In both sets of profiles the nodular masses in the chest are clearly demonstrated by local increases in radioactivity. From these a diagnosis of functioning thyroid metastases seems clear. Residual thyroid tissue in the neck is also demonstrated. The large tracer dose in this and the previous case was used in an attempt to insure uptake sufficient for detection of small metastatic masses situated deep in the chest.

**Discussion.** The cases discussed show that systematic measurements of iodine uptake and plotting of "profile"

curves not only demonstrate the presence or absence of thyroid tissue, but also give information about its relative size and distribution. However, external measurements of radiation cannot be used definitively in the diagnosis of thyroid disease. Certainly in the neck, one cannot distinguish between colloid cyst and metabolically inactive carcinoma, nor between adenoma and active carcinoma. Furthermore, an inactive tumor surrounded by normal thyroid tissue may be confused with an active one. The method is therefore valid only for preliminary studies and should be supplemented by biopsy and radioautograph.

**Summary:** 1. A method for measuring and recording localized collections of administered radioisotopes is described.

2. The use of the method in representative cases of thyroid disease is shown and the limitations are discussed.

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# ANTIGEN TRACER STUDIES AND HISTOLOGIC OBSERVATIONS IN ANAPHYLACTIC SHOCK IN THE GUINEA PIG \*

## Part I

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ONE of the most disputed aspects of anaphylactic shock is the location of the antigen-antibody reaction. Two main theories have developed regarding the reaction site. The cellular theory states that the antigen combines with antibodies fixed to cells, while the humoral theory maintains that the reaction occurs with antibodies in the circulating blood.

By using an antigen labeled with radioactive iodine and employing tracer techniques, we have been able to locate significant antigen concentrations during anaphylactic shock.

The finding of antigen localized in edematous bronchial fibrous tissue suggested our subsequent study to determine the relation of this localization to bronchial obstruction, which is such a striking feature in death of guinea pigs from anaphylactic shock. In this work we studied the stages in the development as well as the final picture of bronchial obstruction during shock and also the bronchial obstruction produced by various pharmacological agents acting on smooth muscle.

**Materials and Methods.** *Antigen preparation.* Partial iodination of bovine gamma globulin† with  $I^{131}$ , radioactive isotope of iodine‡, gives a stable, radioactive, antigenic compound. An alteration in the antigenic specificity of a completely iodinated protein has been described by Wormall,<sup>11</sup> but we found no change in antigenicity resulting from only partial iodination.

A modification of the iodination technique described by Fine and Seligman<sup>7</sup> was used. In preparing the iodine solution, carrier iodine was used in addition to  $I^{131}$  to give color to the solutions and thereby facilitate extraction. To a sodium-iodide solution sufficient to give 1 mg.  $I^2$  we added approximately 20 mc. of carrier-free  $I^{131}$ ; then we added a few drops of hydrochloric acid and sodium nitrite to change the iodide to free iodine. The iodine was first extracted from this solution with carbon tetrachloride, then in turn extracted from the carbon tetrachloride by the following alkaline protein solution: 0.1 gm. of bovine gamma globulin dissolved in a mixture of 1.8 cc. water and 0.5 cc. 20% sodium carbonate. The iodinated protein solution was dialyzed against cold running tap water for 48 to 72 hours. Between 25% and 30% of

\* This work was done under Contract from the Office of Naval Research.

† Bovine gamma globulin Fraction II has a mol. wt. of approximately 150,000. It is homogeneous in electrophoretic behavior. The material used in these experiments was generously supplied by Armour and Company, Chemical Research and Development Department, Chicago, Illinois.

‡ The radioactive iodine used in this work was supplied by Oak Ridge National Laboratories, Oak Ridge, Tennessee.

the  $I^{131}$  used was incorporated in the protein molecules, an average of 3 iodine atoms per molecule of protein. About 5% of the iodine was lost in the two extractions and 65% to 70% failed to unite with the protein and was removed by dialysis. After 48 to 72 hours of dialysis, less than 1% of the remaining iodine could be found in the protein-free filtrate.

The iodine was tied to the tyrosine molecules in the two ortho positions relative to the hydroxyl group.<sup>11</sup> The stability of this chemical linkage was tested by Fine and Seligman,<sup>7</sup> who found that trypsin hydrolysis at 37°C and pH 8 for 6 hours released only 4% of the  $I^{131}$  from the protein. We found that after 24 hours at room temperature in aqueous solution at pH 10.5 only 0.5% of the  $I^{131}$  was split from the protein and at pH 5 only 1.3%. Twenty-four hours in any of the organic substances used in tissue preparation of autoradiograms (absolute alcohol, dioxane, ether, and paraffin) removed less than 3% of the  $I^{131}$  from the protein. Thus, it seemed to us safe to assume that the  $I^{131}$  protein linkage was stable under the experimental conditions.

**Experimental Procedures.** Twenty-six male guinea pigs weighing from 300 to 350 gm. were used in preliminary antigen assays and antigen tracer experiments. Ten were used to determine the range of minimal lethal anaphylactic shock doses using non-radioactive iodinated protein prepared as described above without the addition of  $I^{131}$ .

Nine were given sensitizing injections intraperitoneally consisting of 60 mg. of non-radioactive iodinated protein. After a period varying from 2 to 5 weeks, minimum lethal shock doses (from 2.5 mg. to 10 mg.) of radioactive iodinated protein were injected into the left femoral veins. Shock was fatal within 5 to 8 minutes to all but 2 pigs, which were killed by a blow to the head 8 minutes after injection.

Seven non-sensitized control pigs were given intravenous injections of radioactive antigen (from 2.5 to 15 mg.) and killed by a blow to the head 8 minutes later.

In order to study the mechanism of bronchial obstruction, we used 21 additional guinea pigs. Ten were given sensi-

tizing and shock injections as in the antigen tracer experiment above but were killed in various stages of shock from 1 to 4 minutes after the injection of the shock dose. Six were injected intravenously with fatal doses from 0.2 to 0.5 mg. of histamine. Five were given fatal intravenous injections of 0.1 mg. of Doryl.

Our control animals were killed by either a blow to the head or by intraperitoneal injection of nembutal. The cause of death did not affect the appearance of the lungs.

Histologic study of all the animals was carried out with special emphasis on the site of antigen concentration and mechanism of bronchial obstruction.

Two techniques were employed to locate the antigen within these guinea pigs. First, the amount of radioactivity per gram of blood, lung, liver, spleen, lymph node, striated muscle, kidney, thyroid, brain, and testis was determined by use of a Geiger counter. Error due to self-absorption was eliminated by filtration equivalent to 1.75 mm. of aluminum calculated to stop all beta radiation from  $I^{131}$  and allow only the gamma rays to be counted. Second, the histologic location of the antigen was determined by autoradiograms made from the only two organs containing significant amounts of radioactivity: the lung and liver. Autoradiograms were made according to Evans's<sup>6</sup> method, by slicing tissues at 0.2 cm., fixing in alcohol formalin, and blocking in paraffin in the routine manner. Sections were mounted on lantern slide photographic plates, and allowed to expose in absolute darkness. Exposures varied according to the amount of radioactivity in the tissue and were calculated from Geiger counts of the sections. With filtration equivalent to 0.3 mm. of aluminum, sections registering .05 to .1  $\mu$ c. gave satisfactory exposures in 2 to 3 weeks. After exposure the paraffin was removed from the sections with xylol and the plates were developed according to the usual method. Finally the sections were stained with Harris hematoxylin and mounted.

In an autoradiogram, radioactivity is evidenced by black granular silver deposits (Figs. 1 and 2). The sections show fair histologic detail, although the gelatin



emulsion of the lantern slide stains lightly, giving a blue background to the preparation which makes photography difficult.

**Observations.** Using sensitizing intraperitoneal injections of 60 mg. of non-radioactive iodinated protein and a 2-week sensitization period, we found the range of minimum lethal intravenous anaphylactic shock doses to be

between 2.5 mg. and 5 mg. iodinated protein. Extension of the sensitization period to 6 weeks did not change this minimum range significantly.

The shock produced by this antigen was of the classic type. It began with sneezing and coughing, then development of a "lion's mane," respiratory difficulty, motor activity, convulsions,



Fig. 1.—Autoradiogram of a bronchus from a guinea pig dying in anaphylactic shock. The location of radioactive antigen is indicated by black granular silver deposit. The large blood vessel at left is filled with antigen. Antigen is also seen concentrated in the fibrous tissue around the bronchus. The smooth muscle immediately beneath the mucosa is conspicuously lacking in activity. This preparation was exposed for 1 week. ( $\times 50$ )



Fig. 2.—Autoradiogram made from same block as seen in Fig. 1. Exposure time of 3 weeks was used to accentuate antigen concentrations. ( $\times 50$ )

incontinence, and death within 5 to 8 minutes.

The autopsy radioactivity determinations of all the organs and tissues showed the greatest antigen concentration to be in the blood. Approximately 70% of the fatal shock dose of antigen injected into the sensitized animal was in the blood at time of death, about 85% of the antigen injected into non-sensitized animals was in the blood 8 minutes after the injection. This means, of course, that all tissues would

small amounts of activity could be explained on the basis of contained blood.

The activity concentrations for blood, lung, and liver are given in Table 1. For each animal the activity in 1 gm. of blood has arbitrarily been set at 100, in order to establish a base line for comparison, and the values for lungs and liver calculated accordingly. The activity concentration in the lungs of animals dying in shock was about twice that in the lungs of the controls. The

TABLE 1. ACTIVITY DETERMINATIONS ON BLOOD, LUNG, AND LIVER BASED ON ACTIVITY PER GRAM OF TISSUE

For each animal the activity of the blood is set at 100 and the activities of lung and liver are calculated accordingly.

<i>Non-Sensitized Control Guinea Pigs</i>					<i>Sensitized Guinea Pigs with Fatal Shock</i>				
Animal	Protein Injected (mg.)	Blood	Lung	Liver	Animal	Protein Injected (mg.)	Blood	Lung	Liver
120	3.4	100	43	40	110	7.5	100	57	38
121	3.4	100	31	50	113	10	100	87	64
128	2.5	100	31	36	114	2.8	100	69	34
129	5.	100	37	44	115	5	100	55	24
130	2.5	100	31	40	122	2.8	100	56	37
137	15	100	28	39	123	2.5	100	56	36
138	10	100	33	48	124	5	100	63	37
Average		100	33	42	Average		100	63	39

<i>Sensitized Guinea Pigs with Non-Fatal Shock</i>				
Animal	Protein Injected (mg.)	Blood	Lung	Liver
111	5	100	22	43
117	2.5	100	22	55
Average		100	22	49

show some radioactivity because of the contained blood. Of all the tissues examined, only lung and liver showed significant concentrations of radioactivity.

A significant part of the radioactivity in the liver and a smaller part of that in the lungs was due to the presence of blood containing activity. However, since these organs contained a much greater activity concentration than other vascular organs, such as spleen and kidney, they also had a specific uptake of antigen. The tissues other than lung and liver had only traces or, rarely, small measurable amounts of activity, up to 30% of the amount found in the liver. These

livers of both groups, however, contained nearly equal concentrations of activity. The 2 sensitized pigs which in spite of apparently adequate shock doses did not have fatal shock, had only two-thirds the lung activity concentration found in the controls and about one-third that found in their fatally shocked mates. The livers of these animals showed a slightly higher activity concentration than those of other animals.

Autoradiograms of lungs and livers of these non-sensitized controls and of the sensitized guinea pigs revealed several important findings.

The lungs of the non-sensitized animals showed considerable activity with-

in the blood vessels but no appreciable amount in the tissue. However, the lungs of the sensitized pigs dying in shock showed, in addition to the activity within the blood vessels, a marked concentration of activity in the fibrous tissue surrounding the bronchi and their accompanying pulmonary arteries (Figs. 1 and 2).

The heaviest concentrations of radioactivity were in the edematous, congested, fibrous tissue between the bronchus and its accompanying artery and between the cartilaginous plates and smooth muscle sphincter of the bronchus. The smooth muscle about the bronchi and about the vessels contained no activity. The submucosal tissues and the mucosa of the bronchi contained very little radioactivity. This concentration of radioactivity had a somewhat irregular distribution, varying in amount both in bronchi of the same size and in different levels of the same bronchus. Almost all of the activity was found around bronchi large enough to have cartilage in their walls and the size of these bronchi appeared to have little to do with the amount of antigen concentration. The smaller bronchioles without cartilage and with little surrounding fibrous tissue only rarely had concentration of radioactivity in their walls. There was no significant amount of activity in the alveolar walls or interlobular septa.

In the lungs of the 2 sensitized pigs which did not develop fatal shock there was no significant concentration of activity about the bronchi or elsewhere.

The autoradiograms of the livers of both sensitized and non-sensitized animals were essentially the same. There was definite concentration of the radioactivity within the large blood vessels, but elsewhere there was more or less homogeneous scattering of less intense activity without any concentration in any particular part of the lobule or of

the portal areas. There was a slight suggestion of concentration of the activity about the Kupffer cells, but accurate localization to such small structures was beyond the limitations of the technique.

The histologic study of these animals was directed primarily to the organs of antigen concentration: the lung and liver. The livers of control and shocked animals were indistinguishable. The lungs of these 2 groups, however, differed in several ways. After opening the thorax, the control lungs collapsed immediately to about  $\frac{1}{4}$  the volume of the thoracic cavity while the shocked lungs remained fully distended as a result of the bronchial obstruction. On microscopic examination of the lungs of the fatally shocked guinea pigs, the alveoli and the air passages extending proximally as far as the small bronchi with associated cartilage plates, were widely distended with air. These same structures in normal, control lungs showed various degrees of collapse with consequent thickening of alveolar walls. The lumen of the bronchial tree proximal to the termination of the cartilage plates was approximately the same in both shocked and control pigs and therefore could not be accepted as a measure of the patency of the bronchial tree during life (Figs. 3 and 4). The smooth muscle of both appeared similar and the mucosa was thrown into tall folds which filled the lumen.

There was an important difference, however, between the peribronchial tissues of the shocked and control lungs. The fibrous tissue which surrounded the bronchi and their associated vessels and cartilage plates was normally a thin compact layer of collagenous fibers in which were found irregularly distributed small aggregates of lymphocytes and a network of inconspicuous capillaries and lymphatics (Fig. 3). In the shocked lungs, however, this tissue was distended to 3 to 5 times normal width

by intense edema in which were found enormously congested capillaries and lymphatics and a few scattered lymphocytes (Fig. 4). The edema and congestion were present around all bronchi with cartilage and occasionally around

the smaller divisions but were not entirely uniform throughout. The ratio of amount of edema fluid to bronchial diameter was greatest in the secondary or medium-sized bronchi.

In the series of guinea pigs killed



Fig. 3.—Medium-sized bronchus from normal control animal. The lumen is compromised by infoldings of mucous membrane. The fibrous tissue and vessels around the bronchus are inconspicuous. The cartilage plates are in close proximity to the smooth muscle coat. ( $\times 115$ )

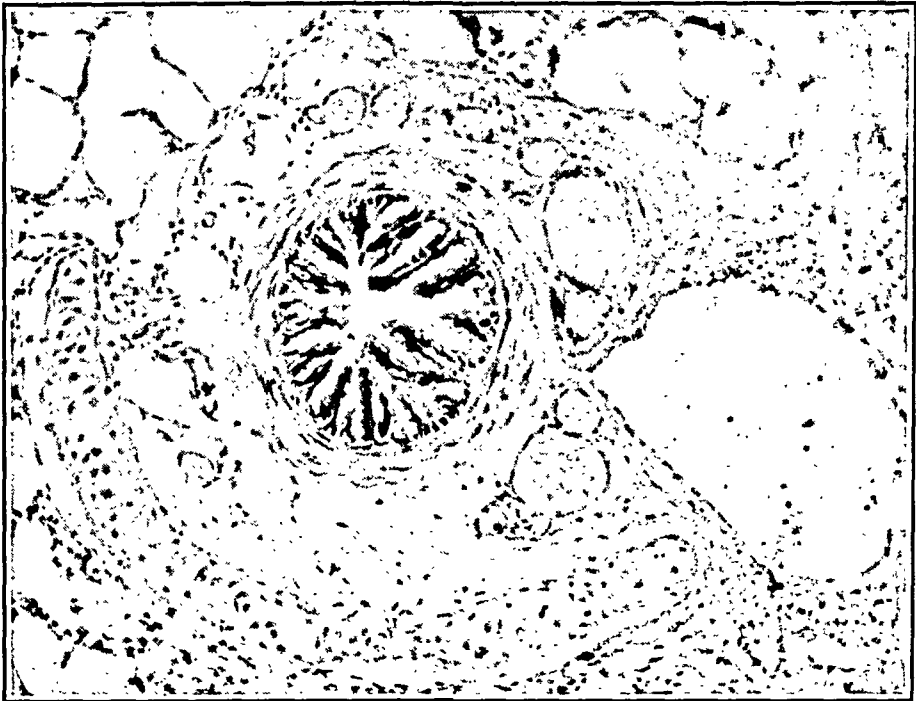


Fig. 4.—Medium-sized bronchus from animal dying in anaphylactic shock. Note close resemblance of lumen, mucous membrane, and smooth muscle to the structures seen in control, Fig. 3. The fibrous tissue is edematous and the blood vessels and lymphatics are congested. The cartilage plate is separated from smooth muscle coat by wide zone of edema. ( $\times 115$ )

at various stages in the development of anaphylactic shock, we traced the pulmonary changes from before the onset of dyspnea to the final stage described above. Dyspnea appeared  $1\frac{3}{4}$  to 2 minutes after injection of the shock dose. Up to this time and at the onset of dyspnea the lungs collapsed on opening the thorax as do normal lungs, but  $\frac{1}{2}$  to  $\frac{3}{4}$  of a minute afterwards the lungs would no longer collapse on opening the thorax, although maximal

but was seen around more of the bronchi. One half to  $\frac{3}{4}$  of a minute following onset of shock there was a definite increase in the amount of edema and congestion, which progressed, and 2 minutes after onset of dyspnea there was  $\frac{1}{2}$  to  $\frac{2}{3}$  the amount of edema seen in the pigs dying of shock.

An interesting, but less easily evaluated, change was apparent in the smooth muscle of the bronchi. Just before the onset of dyspnea, there were



Fig. 5.—Medium-sized bronchus of animal dying 5 minutes after administration of Doryl with marked bronchial obstruction. The lumen of the bronchus is very small and the smooth muscle coat is thick and appears contracted. There is little or no edema. ( $\times 115$ )

distention was not seen until after  $1\frac{1}{2}$  to 2 minutes of dyspnea. Lungs were examined microscopically at the following intervals: (1) 1 to  $1\frac{1}{2}$  min. after shocking dose before onset of dyspnea; (2)  $1\frac{3}{4}$  to 2 min. after shocking dose at onset of dyspnea; (3)  $2\frac{1}{2}$  to  $2\frac{3}{4}$  min. after shocking dose  $\frac{1}{2}$  to  $\frac{3}{4}$  min. after onset of dyspnea, and (4)  $3\frac{1}{2}$  to 4 min. after shocking dose  $1\frac{1}{2}$  to 2 min. after onset of dyspnea.

The bronchial congestion and edema previously described had already started to form around some of the bronchi before respiratory difficulty was evident. With the onset of dyspnea, the bronchial edema was not more marked

irregular thickenings and contraction bands in a few of the smooth muscle sphincters apparently representing a mild degree of contraction. The number of bronchi thus involved increased and was at a maximum  $\frac{3}{4}$  of a minute after dyspnea appeared. The number of bronchi with evidence of smooth muscle contraction was somewhat less 2 minutes after the onset of dyspnea, and at time of death some 2 to 4 minutes later there was no evidence of smooth muscle contraction.

Both of these changes described above would presumably cause a progressive rigidity of the bronchus which would interfere with its function.

**Effects of Pharmaceutical Bronchial Constrictors.** Intravenous histamine injections produced shock similar to but more rapid than anaphylactic shock. The lungs from these animals dying 2 to 4 minutes after histamine injection were morphologically similar to those from cases of fatal anaphylactic shock.

Of the various parasympathomimetic drugs used, pilocarpine, physostigmine, and Doryl, only Doryl produced sufficient bronchial obstruction to keep the lungs distended after the thorax was opened. The degree of bronchial obstruction in these lungs was greater than that seen in anaphylactic shock and was caused solely by a marked contraction and thickening of the bronchial smooth muscle coat (Fig. 5). There was no bronchial edema or congestion. The degree of smooth muscle contraction in these lungs was much greater than that seen in the shocked pigs as indicated by markedly increased thickening of the smooth muscle coat and more definite contraction bands.

**Comment.** In anaphylactic shock caused by intravenous injection of minimal lethal shock doses of iodinated bovine gamma globulin, about 70% of the antigen is found in the blood at time of death. This represents an escape of twice as much antigen from the circulation as occurs in non-sensitized animals in the same time interval.

There was a specific increase in antigen uptake in the lungs after sensitization. Sensitized lungs took up twice as much antigen as control lungs in an equal time. The other organs and tissues did not show any change in affinity for antigen after sensitization. The antigen was found in the loose, edematous bronchial collagenous connective tissue. A part of the antigen found in this edematous region could be explained on a non-specific basis, due to protein containing fluid leak-

ing from the blood vessels. However, control studies with non-specific labeled proteins in the blood stream during anaphylactic shock indicated that such protein leakage in the edema formation does not account for the entire antigen concentration around the bronchi.

The antigen concentration and distribution and the histologic appearance of the liver were the same in sensitized and control animals. This suggests a non-specific phagocytic reaction on the part of the liver since it was unchanged by sensitization or shock.

We did not find satisfactory histologic evidence to support the usual assumption that bronchial obstruction in anaphylactic shock is due solely to smooth muscle contraction. This assumption has been based largely on 2 observations: first, the histologic observation of bronchial stenosis in fatally shocked guinea pigs, which was interpreted as due to smooth muscle contraction. In 1910 Auer and Lewis<sup>2</sup> as well as Anderson and Schultz<sup>1</sup> found fatal asphyxia in anaphylactic shock in guinea pigs, which they thought to be due to bronchial obstruction resulting from contraction of bronchial smooth muscle. Schultz and Jordan,<sup>10</sup> and Biedl and Kraus,<sup>3</sup> noted no great difference between the bronchial lumens and smooth muscle of control and shocked lungs. But in spite of this observation they, too, assumed the bronchial obstruction in anaphylactic shock was due to smooth muscle contraction. Although bronchial edema was noted by some of these workers,<sup>10</sup> it was not considered to contribute to the bronchial obstruction.

Second, the fact that bronchial obstruction resulted from perfusion of partially and completely isolated sensitized lungs with the specific antigen,<sup>4</sup> was interpreted in the light of the

Schultz-Dale phenomenon as being due solely to smooth muscle contraction. Such an interpretation is not, however, conclusive.

Since the fatally shocked lungs had obvious bronchial obstruction, evidenced by their failure to collapse after opening the thorax, one would expect their bronchi to be more constricted than those of normal lungs. Such, however, was not the case, and bronchi in both fatally shocked and control lungs had approximately the same internal diameters, and appeared to be equally compromised by large infoldings of mucous membrane. It is clear therefore that the size of the bronchial lumen seen in microscopic sections cannot be accepted as a measure of the patency of the bronchial tree during life. The smooth muscle in both types of lungs also appeared the same with no convincing evidence of contraction in the shocked lungs. There was, however, a significant difference in the bronchial fibrous tissue, which in the controls was compact and inconspicuous but in the shocked animals was distended with edema to 3 to 5 times its normal thickness. It seemed probable that the extreme rigidity and associated compression of the bronchi caused by the edema could account for most of the bronchial obstruction evident in the shocked lungs.

Study of the stages in the development of anaphylactic shock showed evidence of smooth muscle contraction, thickening of the muscle and contraction bands, only in the early stages, just preceding and for 2 minutes immediately following the onset of dyspnea. At the time of death, 5 to 8 minutes after antigen injection, there was no evidence of smooth muscle contraction. In more rapidly fatal anaphylactic shock produced by egg albumin where death occurs in 2 to 3 minutes, bronchial edema similar to that described here is present, but there is also evidence of smooth mus-

cle contraction about the bronchi at time of death. These observations are supported by Manwaring's work on anaphylactic shock in the dog.<sup>9</sup> He found that the smooth muscle of the uterus, bladder, and intestine began to contract 45 to 75 seconds after the shock injection. The contraction reached a maximum in 2 minutes, and then began to subside. Thus it would seem that smooth muscle contraction in anaphylactic shock might be transitory, occurring in the first few minutes of shock. If shock is fatal within this period, bronchial smooth muscle contraction as well as edema is evident. If, however, the shock is more prolonged, as in our experiment, the degree of contraction of the smooth muscle diminishes and at time of death there may be no evidence of smooth muscle contraction. In such cases the bronchial edema is the only apparent explanation of the bronchial obstruction.

Bronchial edema in the guinea pigs began to form shortly before the onset of respiratory difficulty and increased progressively, being extensive enough 2 minutes later to account for a large part of the bronchial obstruction. At the time of death, this edema was sufficient to account for most, if not all, of the bronchial obstruction.

Bronchial edema was noted by earlier workers<sup>10</sup> and thought to be due to smooth muscle contraction. However, since no edema resulted from the marked bronchial smooth muscle contraction following the administration of Doryl, this conclusion does not appear entirely correct. In studying the anaphylactic reactions of isolated organs in the guinea pig and dog, Manwaring<sup>5</sup> found much perivascular edema, and suggested that the resulting local tissue pressure might be a factor in increased perfusion resistance occurring in shock. He did not, however, suggest that this increased tissue pressure was a partici-

pating factor in bronchial obstruction.

The concentration of antigen in the edematous regions suggests a causal relationship between the presence of antigen, or of the antigen-antibody reaction, and a change in vascular dynamics resulting in the formation of edema.

Because of the antibody storing role of the lymphocytes found by Dougherty, Chase and White,<sup>5</sup> we paid special attention to the lymphoid tissue, especially that of the lung. However, there was no evidence in our material that the lymphoid tissue takes any part in the localization of antigen.

The findings in the 2 non-fatally shocked guinea pigs suggests a decreased affinity on the part of the lungs for the antigen. The possibility of a hyposensitivity, or immunity, in these 2 animals would warrant further investigation.

The exact relation between antigen concentration and edema formation at this time cannot be determined. Investigations are under way now to study interim stages of the edema formation and antigen uptake in the bronchial walls during anaphylactic shock and the effects of various shock preventing drugs on antigen localization and edema formation.

**Summary.** 1. Significant amounts of labeled antigen were picked up only by liver and lung during anaphylactic shock.

2. The amount of antigen taken up

by and its histologic distribution in the liver was the same in sensitized and non-sensitized animals and therefore presumably not related to degree of sensitivity.

3. The affinity for antigen on the part of sensitized lungs in fatal shock was about twice that seen in controls and therefore presumably a function of the sensitivity.

4. The increased amount of antigen taken up by the sensitized lungs was found in the edematous bronchial fibrous tissue.

5. We were unable to confirm the generally accepted assumption that bronchial obstruction of anaphylactic shock results solely from contraction of bronchial smooth muscle. Only in the early stages of shock (within 2 minutes after the onset of respiratory distress) was there convincing morphologic evidence of smooth muscle contraction; and even in these early stages there was already some edema formation. In the terminal stages of shock, the smooth muscle did not appear contracted or otherwise abnormal.

6. The bronchial edema which began to form during the early stages of shock became massive in the terminal stages and at that time appeared to be the most important factor in the production of bronchial obstruction. Since this edematous zone was the site of antigen localization, it seemed possible that the antigen-antibody reaction was related to the edema formation.

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# THE MORPHOLOGICAL BACKGROUNDS OF "GENUINE LIPOID NEPHROSIS"

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In a previous communication<sup>10</sup> I tried to show that the introduction of the concept of "nephrosis" by Müller was an unfortunate one, since at present, students of renal disease are far apart in their interpretation of what is meant by this term. This is manifest in the widely diverse classifications of the "nephroses."

One reason for this conclusion is due to the fact that the original metaphysical concept of Müller has been modified. Beginning as a degenerative and non-inflammatory parenchymatous lesion, nephrosis has at various times been regarded as a series of widely unrelated morphological entities, and at other times a complex of clinical expressions without a precise morphological background.

After numerous vicissitudes the concept suggested by Epstein<sup>4</sup> was widely adopted, namely, that "nephrosis" was a malady characterized by albuminuria, hypoproteinemia, hypercholesterinemia, double refractile lipid droplets in the urine, secondary anemia, edema or anasarca with a low protein content in the exudate, normal renal function and a normal blood pressure, a lowered basal metabolic rate and an exceptional tolerance for thyroid preparations. The morphological background was a "lipoid nephrosis." This is still termed the true or genuine nephrosis. This concept was a direct challenge to pathologists and it did not take long to discover that such a clinical and morphological correlation obtained in only the rarest of instances,

and that in cases where the clinical expression was classic, a "lipoid nephrosis" was not found at post mortem, but usually a glomerulonephritis, less frequently an amyloid kidney, and rarely, the sclerotic kidney associated with hypertension. Nevertheless, despite the presence of glomerulonephritis and amyloid deposits in these kidneys, the organ showed one of the morphological features of a "lipoid nephrosis," namely lipid deposition in the tubules and double refractive bodies in the urine. To reconcile these clinical and anatomical differences, the suffix "nephrotic syndrome" was added. In these cases it was correctly concluded that the lipemia was responsible for the lipid deposition within the renal parenchyma, and that it was not a primary but a secondary event. Furthermore, it was soon discovered that many of the characteristic clinical features of a "lipoid nephrosis" occurred in extra-renal conditions, such as protein starvation, war edema, hepatic cirrhosis, in slow prolonged bleedings from whatever cause, in pernicious anemia, in prolonged ulcerative intestinal lesions and in sprue; and even in these, the kidney at post-mortem showed a greater or lesser degree of lipid deposition. The common denominator in all these conditions was a hypoproteinemia, the result either of loss (albuminuria), deficient intake (hunger edema), failure of formation (liver cirrhosis), and probably, deficient absorption (sprue). That an anatomically perfect "lipoid

nephrosis" may be the result of an extrarenal factor is illustrated in the following case:

Case I. J. H. (adm. 379773) male, aged 43, was admitted to the first medical service (Dr. George Baehr) on Jan. 28, 1933. Following pneumonia, he developed a persistent edema, first of the right leg, then of the left and finally of the abdominal wall. It was thought that the lower part of the inferior vena cava was involved by a thrombophlebitis which had extended upward from the femoral veins. Later the phlebitic process extended to the right jugular vein and to the axillary veins. He returned a year and a half later because of the persistent edema. The urine then showed 3 plus protein and granular casts. The blood pressure was 120 systolic and 75 diastolic. The blood urea was 19 mgm. per 100 cc.

The total blood protein 5.2 gms. %, the blood cholesterol 734 mgm. per 100 c.c., the basal metabolic rate was minus 21%. It was thought that the patient had a subacute glomerulonephritis in the nephrotic phase. In spite of diuretics the edema did not improve. He was again discharged but returned three months later. The edema was very marked. The physical findings were similar to those found on the previous admission. He developed erysipelas and died.

Necropsy (no. 9587). Lipoid nephrosis, old thrombosis with recanalization of the inferior vena cava, renal, left adrenal, spermatic, common iliac, femoral and superior mesenteric veins.

Microscopic findings: The kidney parenchyma showed extensive deposition of fat. The epithelium of the tubules was flattened and there were occasional areas



Fig. 1.—Kidney from Case 1, appearing clinically as a "lipoid nephrosis" and found to be secondary to a thrombophlebitis of the renal veins.

of round cell infiltration in the cortex; with the exception of an occasional fibrotic glomerulus, the glomeruli were intact. There was slight increase in the interstitial connective tissue and some congestion between the tubules (Fig. 1).\*

Epstein's admirable contribution was the application of Starling's<sup>16</sup> law to the explanation of most of the clinical phenomena of "lipoid nephrosis." His contention that the hypoproteinemia was the basic factor in the production of edema and anasarca has received full clinical and experimental confirmation<sup>6,7,8</sup>. This law also explains many of the edemas of extrarenal origin. The mechanisms whereby a hypoproteinemia may cause edema have been summarized in a previous paper<sup>11</sup>.

That the lipemia bears some relation to the hypoproteinemia is acknowledged, the proof being that it has been experimentally produced by plasmaphoresis, by bleeding and by experimental protein starvation. The kidneys under such circumstances also revealing lipid deposition. The precise mechanism is not clear. There is a curious relation between the lipemia and the lowered basal metabolic rate so uniformly found in hypoproteinemic states. I submitted evidence<sup>12</sup> that the lowered metabolism in "nephrotic states" could be explained by the edema which, acting as a suit of clothes, prevented the dissipation of heat from the body. In fact, it was shown that any integumentary thickening was often accompanied by a low basal metabolic rate; for instance, ichthyosis, the edematous stage of scleroderma, certain cases of congestive failure without dyspnea or tachycardia and true myxedema. In these conditions, a lipemia as represented by a hypercholesterinemia was almost invariably present. The lipemia accompanying lowered metabolic rates

possesses all the ear marks of a compensatory phenomenon, but the precise mechanism is unknown. The genesis of lipemia in "lipoid nephrosis" may be represented by this sequence of events: hypoproteinemia → edema → lowered basal metabolism → lipemia (hypercholesterinemia).

The purpose of this discussion is to show that the lipid deposition in the renal parenchyma is secondary to the hyperlipemia and that therefore a "lipoid nephrosis," in the anatomical sense, is not primary and therefore cannot be the background for the clinical manifestations, but rather, that it is the result of physico-chemical mechanisms sequential to a hypoproteinemia.

Divorced of a consistent morphological background, "lipoid nephrosis" loses its status as a disease, and is relegated to being a syndrome comprising clinical phenomena which may be both renal or extrarenal in origin.

Even as a clinical entity, "lipoid nephrosis" has been shown to lack the sharp differentiation from glomerulonephritis that its sponsors formerly contended. This has come about through the biological study of the disease. It was held that "lipoid nephrosis" differed from glomerulonephritis in two particulars, first that hypertension was lacking and, second, that "lipoid nephrosis" was not associated with renal insufficiency. A study of the biology of "lipoid nephrosis" has amply shown by adequate follow up that an appreciable number of such cases develop both hypertension and renal insufficiency.<sup>3,9,14,15</sup> This does not imply that a new malady has been superimposed, because at post-mortem the typical morphological evidences of glomerulonephritis were found. The presence or absence of hypertension is

\*This case will shortly be reported by Gerber and Moschkowitz in a paper on "visceral thrombo-phlebitis migrans."

important in the differentiation between "lipoid nephrosis" and glomerulonephritis; but whether it is present throughout the course of every glomerulonephritis is an open question, because we are not always in a position to study every case throughout its life cycle. But that hypertension is lacking at some particular cross section of this cycle is a familiar observation. The same reasoning applies to the presence or absence of renal insufficiency. In the final analysis, these differentials are subject to a time factor.

**Morbid Anatomy.** The specificity of "lipoid nephrosis" as a distinct disease has been based on the paucity or even absence of the productive morphological changes within the glomeruli conventionally viewed as characteristic of glomerulonephritis. In view of the close clinical mimicry between "lipoid nephrosis" and the nephrotic form of glomerulonephritis, some have suspected that "lipoid nephrosis might be one of the anatomical results of a glomerulonephritis. There has been much controversy about the interpretation of the glomerular changes that have been observed in "lipoid nephrosis" and pathologists found it difficult to understand how a lesion like glomerulonephritis, so unmistakably of a productive nature, could evolve into a lesion in which the changes in the glomeruli were so minimal or even absent. Bell<sup>1</sup> revived the controversy in 1929 and by employing the histological technique of Mc Gregor he described in four cases of "lipoid nephrosis" a thickening of the basement capillary membrane and a varying increase in the number and size of the glomerular endothelial cells. These lesions he interpreted as evidences of a glomerulonephritis. Bell's conclusions have been criticised on the ground that none of his four cases appeared to be unalloyed instances of pure clinical "lipoid nephrosis." The entire problem depends upon whether

our knowledge of the evolution of the morbid anatomy of acute glomerulonephritis is complete. We are well informed in the clinically progressive cases, whether or not associated with a "nephrotic component," but we are still unacquainted with the morphological appearance of such a kidney in apparently healed cases. Furthermore, clinicians have known of clinically established cases of acute glomerulonephritis that lose their hypertension and renal insufficiency and pass into a subacute phase in which the only clinical evidence of a renal disorder is a proteinuria of a considerable degree; in time, such patients eventually develop the classical clinical manifestations of a "lipoid nephrosis." The clinical continuity does not again permit us to say that a new disease has been superimposed. What lesions may we expect to find under such circumstances? Opportunities to observe such a sequence of events and a post-mortem examination come but rarely, and so we feel privileged to report such a case.

**Case 2.** (Adm. 461645). R. H., age 3 years, was first admitted to the Pediatric service (Dr. B. Schick) of the Mt. Sinai Hospital, December 3, 1939. She had been sick with fever and sore throat for a week, swelling of face and abdomen for 2 days, and red urine for 1 day. There was moderate swelling of face and legs. The temperature was 103° F. but returned to normal the next day. There was evidence of receding tonsillitis. The blood pressure was 140 systolic and 100 diastolic; the blood urea nitrogen was 8 mg. per 100 cc.; the serum protein was 5.1 gm. %, of which the albumin fraction was 3.8 gm. %. The urine contained albumin 2 plus, red blood cells and few casts. On December 5, it was noted there was no gross blood in the urine. On discharge, December 19, 1939, albumin had disappeared from the urine.

**Second admission** (March 12, 1940). Three weeks before admission generalized edema was noted. The blood pressure was 124 systolic and 90 diastolic; the

blood urea nitrogen 9 mg. per 100 cc.; the total serum protein 4.5 gm. %, of which the albumin fraction was 2.5 gm. %; and the cholesterol 550 mgm. per 100 cc. During her stay in the hospital the edema persisted, the urinary albumin was 3 plus, the cholesterol was high, on one occasion attaining 1050 mg. per 100 cc. The blood pressure remained about the same. The patient was discharged August 6, 1940.

Third admission (August 25, 1941). No clinical improvement was noted during her home stay. The blood pressure was 110 systolic and 85 diastolic. The serum protein was 3.3 gm. %, of which the albumin fraction was 1.5 gm. %. The blood chemistry was the same as on the last admission. The child had erysipelas twice. She died of a pneumococcic peritonitis on January 12, 1941. The

urine always contained 4 plus albumin with a few red blood cells and rare casts. Two weeks before death the blood urea nitrogen was 28 mg. per 100 cc.

Necropsy (no. 11728). Microscopic examination. The renal architecture of the kidney seems not to be profoundly disturbed; however, throughout the cortex one sees small foci of tubular atrophy with increased stroma and frequently one sees the stroma widened with infiltration by lymphocytes with occasional polymorphonuclear leukocytes.

The proximal convoluted tubules are quite distended and contain a considerable amount of albumin. The epithelial cells generally show a good brush border and the cytoplasm is finely granular. The terminal portions of the convoluted tubules contains a large amount of pink granular material which is probably albumin. The



Fig. 2.—Kidney from Case 2, that clinically began as a glomerulonephritis and termed clinically as a "lipoid nephrosis," showing a glomerulus partially adherent to the glomerular capsule.

epithelium in such portions shows vacuolization. Glomeruli: A superficial examination of the glomeruli seems to indicate that they are not materially altered. However, if one examines more carefully, one finds certain changes affecting the majority. The lobulation of the tuft is exaggerated and the lobules appear rather plump. The basement membranes of the capillary loops are thick and there is fusion of such loops with each other and with the capsule. Some glomeruli show multiplication of the capsule epithelium. The Bowman's space contains only a small amount of albumin (Fig. 2).

**Epicrisis.** While not completely satisfying the criterion of a true anatomical "lipoid nephrosis" in that most of the glomeruli show minimal changes, the kidneys correspond closely to those described by such ardent sponsors of the disease specificity as Fahr<sup>5</sup> and Munk<sup>13</sup> even in regard to their focal distribution. In other respects the histological changes of the previous glomerulonephritis had completely resolved. These kidneys, in other words, might be regarded as instances of "lipoid nephrosis," provided we had not known that the patient had previously passed through a classical attack of glomerulonephritis. On his third admission, his hypertension had disappeared, so that had this patient been seen for the first time during his third admission, the diagnosis of "lipoid nephrosis" would have been justifiable.

The succeeding case is presented because the sequence of clinical events was the reverse of the preceding.

**Case 3.** S.M. (adm. 244959) male, aged 8, was admitted to the Pediatric service (Dr. B. Schick) of the Mt. Sinai Hospital for the first time on Nov. 20, 1921. He presented at that time a general anasarca of 6 weeks' duration with a pronounced proteinuria and casts. The blood pressure was 100 systolic and 80 diastolic, the blood urea nitrogen varied between 16 and 19.6 mg. per 100 cc. The serum protein was 4.2 gm. per 100 c.c. and the blood cholesterol was 682 mg. per 100 cc.

The basal metabolic rate was minus 30%. The diagnosis of "lipoid nephrosis" was made. Six months later he returned with glandular swelling of the neck, an enlarged spleen, slight fever and a lymphocytosis. A diagnosis of infectious mononucleosis was made. The anasarca and the marked proteinuria was still present. The blood urea nitrogen was 14 mg. per 100 cc., the blood cholesterol 630 mg. per 100 cc., and the blood pressure was 105 systolic and 60 diastolic. His third admission occurred 15 months later for an upper respiratory infection. The blood pressure on this admission was 145-100 mm. Hg. The blood urea nitrogen was 30.8 mg. per 100 cc. The blood cholesterol was 356 mg. per 100 cc. About 9 months later he was again admitted. Two days previously he had abdominal pain with vomiting. Aside from the general anasarca he had signs of peritonitis. The blood culture showed a pneumococcus type iii. There was fever up to 103° F. for 3 days after admission. The signs of peritonitis disappeared, but he developed an abscess in the lumbar region which was incised. He remained in the hospital for over 5 months. The blood pressure varied between 90 and 124 systolic and 50 to 80 mm. Hg. diastolic. On discharge it was 100 systolic and 70 diastolic. The blood urea nitrogen was 30.8 mg. per 100 cc. on admission but thereafter it was normal. The blood cholesterol varied between 170 to 260 mg. per 100 cc. The proteinuria had diminished appreciably during his stay, and the anasarca disappeared. The basal metabolic rate was practically normal showing 33-35 calories per kilo of body weight. The fifth and last admission occurred about 5 months later (April 12, 1925) and about 3½ years after the first admission. Two days previously he had chills and high fever due to an extensive cellulitis of the thigh and abdominal wall. The blood culture showed pneumococci. There was general anasarca, a marked proteinuria and a blood cholesterol of 334 mg. per 100 cc. The blood pressure was 100 systolic and 60 diastolic. He died 3 days later.

**Necropsy findings.** Microscopically, there is diffuse tubular degeneration with

abundant fat droplets in the epithelium. In numerous places these degenerated cells have undergone calcification. In a very few areas, the capsule of Bowman is definitely thickened and the glomerular cusps are adherent. There are numerous areas of round cell infiltration of the cortex (Fig. 3).

**Epicrisis.** This patient's clinical manifestations at the first examination were those of a typical "lipoid nephrosis." Inasmuch as the reason for his entry was a generalized edema, the disease must have begun probably many months before. On his third admission, a definite hypertension was noted and the diagnosis of "lipoid nephrosis" was abandoned. A fluctuating but moderate systolic hypertension persisted until his last entry and

was associated with a transient infection; a moderate azotemia developed which later subsided. In the final admission, following a pneumococemia, the blood pressure returned to normal, the anasarca and proteinuria was pronounced, there was a slight azotemia. In view of the glomerular changes, however slight, one must conclude that this patient suffered from a glomerulonephritis from the onset. The glomerular changes we have described are reported by such advocates of "lipoid nephrosis" as Fahr<sup>5</sup> and Munk<sup>13</sup> as an anatomical entity and an integral part of the lesion of "lipoid nephrosis." However, inasmuch as the precise changes are observed in occasional glomeruli in otherwise unmis-takable subacute and chronic glomeru-



Fig. 3.—Kidney from Case 3, that began clinically as a "lipoid nephrosis" and terminated as a glomerulonephritis showing round cell infiltration of the cortex and thickening of an occasional glomerular capsule.

lonephritis, it is fair to presume that this viewpoint is arbitrary.

These two cases of glomerulonephritis with minimal glomerular changes and masquerading clinically as "lipoid nephrosis" suggest the possibility that a glomerulonephritis may anatomically resolve, leaving the glomeruli intact. The following is such a case:

Case 4. (adm. 305675) S.L.T. male, aged 2½ years, was admitted to the Pediatric service of the Mt. Sinai Hospital (Dr. B. Schick) on August 14, 1929. There

mm. Hg. The blood urea nitrogen levels remained within the range of normal the highest being 14.0 mg. per 100 cc.

Necropsy (no. 6909): Microscopic examination. The glomeruli are normal. The cytoplasm of the tubules is swollen and show numerous vacuoles. With the microscopic polaroscope many double refractile bodies are visible in the cytoplasm of the tubules and also in the interstitial cells of the kidney. With the fat stain, there are deposits mainly in the tubules and a few in the interstitial tissue (Fig. 4).



Fig. 4.—Glomerulus from Case 4, that clinically was a glomerular nephritis but anatomically the organ revealed a "lipoid nephrosis." The glomerular endothelium is swollen and filled with fat granules but there is no proliferation.

was swelling of the eyelids and face which began 3 months ago. The urine showed a marked proteinuria and some casts. The blood pressure was 100 systolic and 60 diastolic. The P.S.P. showed an excretion of 43% in two hours. The blood urea nitrogen was 10.0 mg. per 100 cc., the blood cholesterol was 346 mg. per 100 cc. The total blood protein on one determination was 7.08 gm. %, one week later it was 5.4 gm. % and a few days before death it was 3.55 gm. %. After 2 weeks the edema subsided. Four weeks later he developed a pneumococcus pneumonia followed by a peritonitis. He died 3 days later. The blood pressure was within the range of normal during most of his stay, but at times it reached 130-90

**Epicrisis.** In the past 25 years, this is the first of the only two cases of true or genuine anatomical "lipoid nephrosis" that have come to post-mortem examination in the Mt. Sinai Hospital. Even here the question arises whether this patient had a previous glomerulonephritis or not. If even a transient hypertension in the course of the illness of the slight degree mentioned above may be viewed as a distinguishing mark of a glomerulonephritis, we would be forced to conclude that an acute glomerulonephritis preceded the morphological picture of a "lipoid nephrosis." Nevertheless despite the



normal appearance of the glomeruli with our modern microscopic technique, their capillary membranes possessed a pronounced permeability for protein. The important light that this case throws upon the evolution of glomerulonephritis is this; that an acute glomerulonephritis may apparently resolve completely in the histological sense, although the clinical manifestations pursue their course.

1928. Six and one half months prior to admission he had been given antiluetic treatment for a 4 plus Wassermann reaction. During this period his urine was albumin free. One week after the last mercury injection he developed sore gums and a generalized anasarca. The Wassermann test was now negative. His blood pressure was 100 systolic and 64 diastolic. The urine showed protein in large amounts, hyaline and granular casts and doubly refractive lipid bodies. The blood



Fig. 5.—Intact glomerulus from a man aged 43 who developed the typical clinical and anatomical manifestations of lipid nephrosis, soon after a course of treatment for syphilis.

The second case of pure "lipoid nephrosis" is presented not only because hypertension was absent throughout the period of observation, but also because of the presumably syphilitic origin of the disease.

Case 6. (adm. 287343) A.M. male, aged 45, was admitted to the second medical service (Dr. B. S. Oppenheimer) of the Mt. Sinai Hospital January 18,

urea nitrogen was 20.0 mg. per 100 cc., the cholesterol 600 mg. per 100 cc., and the total serum protein was 7.0 gms. %. The diagnosis of "lipoid nephrosis" was made and he was given vigorous antiluetic treatment with neosalvarsan and bismogenol. Despite this, the anasarca became progressive. To relieve the extreme edema of the legs, Southey tubes were inserted. Eventually he developed erysipelas and

he died a little less than a month after admission.

**Necropsy (no. 6088): Microscopic examination.** The glomeruli are entirely normal with the exception of a sporadic fibrous glomerulus. In not a single glomerulus is there any proliferation of the capsular or capillary endothelium, and the capillaries are everywhere patent. The capillary walls are thin. The epithelium

after extensive mercurial stomatitis suggests the necrotizing nephrosis of mercury poisoning, rendering the capsules of Bowman permeable to protein. There is no factual evidence that syphilis is the cause of a "lipoid nephrosis."

**Comment.** It is apparent that our knowledge of the histomorphological



Fig. 6.—Tubules from same case as Fig. 5, showing basal vacuolization of the protoplasm and hyaline droplet degeneration toward the lumen.

of the convoluted tubules is swollen, contains large granules, and there are many doubly refractive fat droplets particularly near the basement membrane. In occasional tubules, honeycombed desquamated epithelial cells lie within the lumen (Figs. 5 and 6).

**Epicrisis.** It is difficult to appraise this case. The absence of albuminuria only a few weeks before his admission renders a previous glomerulonephritis most unlikely, but the fact that a profound albuminuria appeared shortly

evolution of acute glomerulonephritis requires revision. Apparently, in some instances, especially in children, the productive changes are so slight that only minimal glomerular changes are produced. In other and much rarer instances the productive changes appear to disappear completely. In the latter case, the anatomical picture of a true or genuine "lipoid nephrosis" results; when minimal lesions of the glomerulus persist we derive what Bell<sup>2</sup> calls the "mixed" form. One merges impercep-

tibly into the other and the end result is quantitative and not qualitative. Pathologists are not in the habit of visualizing glomerulonephritis in this light. The factor or factors which determine the intensity of the glomerular lesion are entirely unknown. These biological sports in the evolution of glomerulonephritis do not permit us to predict the morphological findings from the clinical phenomena, except in the broadest way. We can often predict the amount of lipoid infiltration in the renal parenchyma from the level and duration of the hypercholesterinemia. The extent and maturity of renal damage is only one of the factors in producing renal insufficiency, since this is conditioned by extra-renal factors, notably cardiac failure from an associated hypertension, or a concomitant febrile disorder. According to Bell<sup>2</sup> hypertension does not develop unless the basement membrane of the capillaries become so thick that they become narrowed; and the blood flow is decreased. That this mechanism does not always maintain is shown by the cases with hypertension we have described in which there was either no thickening of the basement membrane, or when it was present, the number of affected glomeruli were so small that the thickening could hardly cause renal ischemia. The cause of the hypertension in glomerulonephritis remains problematical.

**Summary.** The term "nephrosis" has been so modified by subsequent students of the malady from its original connotation, that when it is employed one should demand a definition.

The fundamental clinical phenomena of "lipoid nephrosis" are here reviewed and their genesis outlined. The pri-

mary factor is a prolonged hypoproteinemia. The hypoproteinemia is the result of a persistent proteinuria consequent to an increased permeability of the glomerular capillary walls, which is not always explainable histologically with our current technical methods. The hypoproteinemia, and especially, hypoalbuminemia, is responsible for the edema and anasarca and for the low protein content of the exudate. In addition, the hypoproteinemia is probably indirectly responsible for the low basal metabolic rate by creating an edema which acts as a suit of clothes preventing the dissipation of heat. This explanation is based on our demonstration that integumentary thickenings of whatever nature are usually accompanied by a low basal metabolic rate. The lipemia represents in all probability a compensatory phenomenon.

Evidence has been submitted to show that anatomical "lipoid nephrosis" represents nearly always one of the biological progressions of a glomerulonephritis, in which the conventional productive changes have either disappeared or have not developed. In other instances, it may be the result of extrarenal factors in which a hypoproteinemia ensues.

Clinical and anatomical "lipoid nephrosis" are by no means synonymous. In the last analysis, "nephrosis" is not a disease in the sense that it has a consistent background in either morbid anatomy or etiology. Instead of employing a generic term to cover a multitude of unrelated morphological backgrounds, accuracy of thought would be promoted by ascribing the best available descriptive term for each renal disorder.

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# THE CLINICAL USES OF INTRAVENOUS DIPHENHYDRAMINE HYDROCHLORIDE (Benadryl Hydrochloride)

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Reports on diphenhydramine hydrochloride (benadryl hydrochloride) are in general agreement as to the value of this drug in certain allergic diseases, such as hay fever and urticaria. There is also general agreement as to its lack of efficacy in most patients with bronchial asthma. These 3 allergic conditions comprise the largest percentage of cases in which the anti-histaminic drugs have been used. Most reports include a small number of other conditions, either allergic or questionably so. Some conclusions have been drawn as to the value of the compound used from the results obtained in a small group of patients.

One of the difficulties present in the attempt to evaluate any drug in the treatment of a specific disease is the time interval which must elapse between the administration of the medication and the time the effects are first observed. If the disease is one in which subjective symptoms wax and wane rapidly, it may be impossible to determine the effect of a particular medication.

The purpose of this study is to evaluate the use of an intravenous solution of benadryl\* in the treatment of conditions generally accepted as being allergic as well as in conditions which are questionably allergic in nature. If a medication brings relief within a few

minutes after it is given, the possibility that the relief is directly related to the medication is greater than if there is a time interval of 30 to 60 minutes before relief is obtained. It was felt that the results would be of therapeutic importance and might aid in evaluating the drug in conditions in which its efficacy is questionable.

**Material and Methods.** Thirty-nine patients were treated with easily evaluated symptoms of a possible allergic nature. An intravenous solution of benadryl was used which contained 10 mg. per cc. It has been our practice to use a dilution of approximately 10 mg. per 30 cc. of normal saline. Our usual dose had been 30 mg. of benadryl given by a continuous intravenous drip, taking from 7 to 12 minutes to complete the procedure. Doses of 10 to 50 mg. have been used in appropriate dilutions. The results of the therapeutic trials are listed in Table 1.

**Results. Urticaria.** Twenty-one patients with urticaria were treated. Nineteen of these experienced complete relief of the pruritus immediately. It was interesting to see that the relief of symptoms, if it occurred, followed a certain rather definite pattern. Many patients first noticed diminution in the pruritus when as little as 10 mg. of the benadryl had been received. The relief was centrifugal in nature, first being experienced on the trunk and back,

\* Supplied through the courtesy of Dr. E. A. Sharp; Parke Davis & Co.

then progressing down the extremities until the final points of discomfort were usually the hands and feet. These patients were very much aware of their discomfort due to the pruritus. As this diminished, many of them then complained of a burning sensation. It was felt that this burning sensation was due to the local irritation from scratching and rubbing. This sensation disappeared by the end of the infusion. The wheals also changed as the treatment was being given. In the fair-skinned patient, the red wheal blanched from

patients who did not respond to intravenous benadryl were both patients whose urticaria followed the use of penicillin in wax and oil. It has been our experience that those patients, who have responded, usually have started to do so by the time they have received 10 to 15 mg. of benadryl. Our feeling has been that if the patients did not respond to 30 mg., they would not respond to any dose and treatment with an anti-histaminic agent was then abandoned. This was our procedure in the 2 cases of urticaria which did not re-

TABLE 1.  
CLINICAL RESULTS OF INTRAVENOUS BENADRYL HYDROCHLORIDE  
IN 39 PATIENTS

Diagnosis	No. of Cases	Improved	Not Improved
Urticaria .....	21	19	2
Asthma .....	3	1	2
Vasomotor Rhinitis .....	2	2	
Pruritus with—			
Poison Ivy .....	4	4	
Jaundice .....	1		1
Neurodermatitis .....	2	1	1
Miscellaneous—			
Allergic Arthritis .....	1	1	
Gonorrheal Arthritis .....	1		1
Tabetic Crises .....	1		1
Unilateral Headache .....	1		1
Dysmenorrhea .....	1		1
	39	29	10

the center outward so that at times the wheal would become a raised area comprised of a red rim around a blanched center. The size of the wheal did not usually change immediately but would gradually disappear over a period of about 1 hour.

In some patients the period of relief was only 3 or 4 hours. In others no further medication was required for 6 to 8 hours. All patients relieved by the intravenous benadryl in whom a recurrence of the itching occurred, obtained relief by the use of the drug orally. Three of the patients with urticaria who had relief did not have a recurrence of the pruritus after the initial intravenous dose was given and no further oral therapy was necessary.

It is of interest to note that the 2

spond to intravenous benadryl. However, one of our more recent patients was one who developed angioneurotic edema of the face and lips following antiluetic therapy with penicillin, bismuth and mapharsen. He was given 30 mg. of intravenous benadryl with no change in the angioneurotic edema and little change in the associated pruritus. Following this he was then put on 100 mg. of oral benadryl every 3 hours, with marked relief of symptoms and disappearance of the edema. The response of this patient to oral medication after failure of the intravenous drug has made us realize that in some patients our arbitrarily chosen dose of 30 mg. of the intravenous solution may be insufficient. Any patients who do not obtain relief from 30 mg. intravenously

probably should be given a larger dose before the drug is definitely considered to be ineffective.

**Asthma.** Three patients with severe acute attacks of bronchial asthma were treated with intravenous benadryl, 2 receiving 40 mg. of the solution and 1 receiving 30 mg. In 2 cases there was no appreciable change in the patient's condition; 1 received immediate objective relief. All of these patients had received various other forms of therapy previous to the use of benadryl. There have been reports in which benadryl has proved of value in the treatment of asthmatics but generally the reports have been discouraging.

**Miscellaneous.** Four patients with contact dermatitis (poison ivy) were given intravenous benadryl. All of these patients had immediate cessation of the pruritus. One, after being relieved of his pruritus by an injection of intravenous benadryl, was put on a maintenance dose of 50 mg. orally every 4 hours. He experienced no relief from this medication and the dosage was increased until the patient was receiving 100 mg. every 2 hours. No relief was obtained with these large doses. This is the only patient in our series who was relieved by the intravenous preparation but not by the oral drug. The only explanation felt plausible is that absorption of the drug from the gastrointestinal tract was impaired.

We have recently reported<sup>1</sup> the use of benadryl in 14 cases of poison ivy dermatitis with complete relief of itching in 12 cases and moderate relief in 2. Some authors have reported good results, others poor results in the relief of the pruritus of poison ivy dermatitis by benadryl. It is our opinion that the use of intravenous benadryl is the most objective method of determining the value of the drug in this and similar conditions.

One patient with tabetic crises was

not benefited. Neither were 2 other patients, one of whom had a severe unilateral headache with certain migraineous features and the other who had a chronic gonorrheal arthritis with a painful knee joint. The last 3 patients were included because of the possibility that there might have been an allergic factor in the production of their symptoms.

One patient with pruritus associated with chickenpox was given intravenous benadryl with marked relief from the itching. She was then maintained on oral benadryl with relief. Several other patients with chickenpox also received marked relief from the use of oral benadryl.

Two patients with neurodermatitis were treated. One experienced no relief from the intravenous therapy while the other had marked relief. The patient who was not relieved was given very large doses of oral benadryl without effect. The patient who was relieved was maintained on the oral medication with marked relief from itching and clearing of the skin lesions. Two patients with vasomotor rhinitis experienced complete relief after the administration of intravenous benadryl. One patient with an allergic arthritis of a palindromic nature also was relieved. One patient who had pruritus associated with jaundice was not relieved. One patient with severe dysmenorrhea was not benefited.

**Discussion.** The use of an intravenous preparation of benadryl has not been stressed in many reports. Some authors have found certain specific advantages in using the intravenous mode of administration. McElin and Horton<sup>2</sup> attempted to inhibit the rise of histamine induced gastric acidity in patients with multiple sclerosis by use of intravenous benadryl. They felt that there is suggestive evidence that in some instances the curve of gastric acidity is

altered in patients with multiple sclerosis. Reinstein and McGavack<sup>8</sup> found that oral benadryl had no effect on the glucose tolerance, whereas when given intravenously in 30 mg. doses, benadryl seemed to increase sugar tolerance. Moersch *et al.*<sup>6</sup> studied the gastric secretory response of patients given intravenous benadryl. It had been shown previously that successive equal subcutaneous injections of histamine produced almost identical curves of gastric acid response.<sup>9</sup> This served as a basis for what the authors designated the "double histamine test." After determining if in the original test the curves were similar, a tested material was then introduced between the 1st and 2nd curve. If there is a change in the 2nd curve it is felt that the introduced material may be responsible. After the concentration of hydrochloric acid and the total volume of gastric juice was obtained following subcutaneous histamine, intravenous histamine, and a test meal, in 3 groups of patients, these patients were then given an identical test coupled with the use of intravenous benadryl. There was no material difference found in the volume of gastric content nor in the concentration of free hydrochloric acid after the administration of intravenous benadryl.

McElin and Horton<sup>3</sup> report the use of intravenous benadryl in 26 patients. In urticaria their results were good. One patient with dysmenorrhea was not benefitted. Their results in treatment of patients with hay fever and vasomotor rhinitis were good. In 1 case of acute bronchial asthma intravenous benadryl was tried on 3 occasions without relief. In 3 cases of histamine cephalgia, typical attacks were provoked by giving histamine subcutaneously. As soon as a typical attack had developed, intravenous injection of 60 mg. of benadryl per 100 cc. of physiological saline solution was begun at about 120 drops per minute. On all

3 occasions, relief was obtained promptly; in one, definite and complete relief was obtained in 30 seconds. However, in 8 cases of histamine cephalgia the oral use of the drug seemed to be of only limited value.

**Toxic Effects.** McElin and Horton<sup>3</sup> suggested early in the study of the use of benadryl that the intravenous method of administration was of value in the clinical investigation of the drug. They used doses of 10 to 120 mg. by the continuous drip method. Routinely they recommended the use of 60 mg. in 100 cc. of normal saline solution. With this method they encountered no evidence of acute toxicity. Dizziness, sleepiness, and dry mouth were the significant side reactions. It was noted that dizziness was present in every patient when the sitting position was assumed at the end of the injection. These symptoms were of short duration. McGavack *et al.*<sup>4</sup> reported reactions in 3 of 10 subjects given intravenous benadryl. One patient was given 20 mg. and the other two 30 mg. each, of the drug. The reaction in one patient consisted of weakness, headache, "sea-sickness," and drowsiness, all associated with extreme pallor. No estimation of the blood pressure was given. The 2nd patient complained of dizziness with a sensation of falling to the left which lasted about 1 hour. The 3rd patient developed a severe chill associated with sweating, headache, low back pain and a slight decrease in temperature but with no change in either pulse rate or blood pressure. In this article no mention was made of the dilution factor used. However, one of the authors<sup>6</sup> states that his practice has been to inject the intravenous benadryl undiluted, usually taking from 30 to 90 seconds for the injection. This may account for the high percentage of reactions obtained.

As mentioned, our practice has been to inject 30 mg. in about 75 to 100 cc.



of normal saline by continuous drip, taking from 7 to 12 minutes to complete the injection. Of our 39 patients, 8 experienced side effects. Two were both dizzy and sleepy, 2 were dizzy and 2 were sleepy. One patient had a chilly sensation followed by a mild chill immediately following cessation of the injection. This wore off in about 2 minutes. Another patient immediately following the injection felt sleepy. However, about 90 minutes after the treatment he suddenly developed bilateral low back pain, headache and a shaking chill which lasted about 20 minutes. When this wore off he had no further reactions. In all of these patients, the side effects wore off very quickly. It is felt that the dosage, dilution factor, and speed of administration were responsible for the lack of more toxic effects. That there is a wide safety factor between the therapeutic and toxic doses can be seen from the large doses that have been used. Moersch *et al.*<sup>6</sup> report the use of 200 mg. of benadryl in 200 cc. of normal saline by continuous drip at the rate of 35 to 40 drops per minute. Toxic effects are not mentioned. One of the authors states that no serious toxic effects were noted after use of large doses.<sup>7</sup> McGavack<sup>5</sup> states that he has given as high as 100 mg. intravenously undiluted with no serious side effects. From the results we have obtained, we feel that a usual dose of 30 mg. is sufficient to produce a therapeutic result. If that dose is unsuccessful, then the use of a larger dose is justified. If there is no response to the intravenous drug it is felt that the oral form

of therapy is not indicated.

That intravenous benadryl has a certain therapeutic value is unquestioned. In our opinion the use of this type of therapy is of even greater aid in permitting the quick evaluation of the efficacy of the drug in any particular condition in which the value of the medication is doubted. If relief is obtained with the intravenous preparation, then the oral method of administration should also be effective if large enough doses are given. Frequently the drug has been felt to be ineffective, when in reality it was not being used properly. On several occasions it was found that patients were receiving small amounts of the drug by mouth with little or no relief. These patients were then given intravenous benadryl with immediate relief of symptoms. Larger doses were recommended by mouth and the patients then obtained relief.

**Summary.** Thirty-nine patients were treated with an intravenous preparation of benadryl. The results obtained were similar to those obtained in the use of the oral preparation. The various uses to which intravenous benadryl has been put are reviewed. A dosage and dilution of intravenous benadryl has been recommended. Toxic effects have been discussed and their relation to dosage, dilution and speed of administration have been described. It is felt that one of the most useful purposes of intravenous benadryl is to aid in the immediate evaluation of the drug in any condition in which its value is uncertain.

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# THE EFFECTS OF CERTAIN DIHYDROGENATED ALKALOIDS OF ERGOT IN HYPERTENSIVE PATIENTS\*

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CLINICAL experience with surgery of the sympathetic nervous system has stimulated the search for chemical agents that will effectively inhibit functions of the sympathetic nervous system, particularly vasoconstriction. Among the compounds found to have sympatholytic and vasodilator properties are the tetraethylammonium salts<sup>7</sup>, dibenamine<sup>9</sup>, and pentaquine.<sup>6</sup> None of these agents, however, has proved to be of practical value in the treatment of essential hypertension.

An additional group of sympatholytic agents has been available in the naturally occurring alkaloids of ergot.<sup>4,11</sup> However, these substances do not possess significant vasodilator properties, presumably because of their direct stimulating action on smooth muscle including that of the blood vessels<sup>11</sup>. As a result, they have found no use as therapeutic agents in peripheral vascular disease or in essential hypertension.

Recently Stoll and Hofmann have prepared dihydrogenated derivatives of the ergotoxine group of alkaloids<sup>12</sup> which exhibit marked sympatholytic and adrenolytic properties in animals with only slight direct stimulating ef-

fects on smooth muscle<sup>11</sup>. These compounds are less toxic in animals than the naturally occurring derivatives of ergotoxine and one of them, dihydroergocornine, when administered intravenously has been found by Bluntschli and Goetz<sup>2</sup> to lower the blood pressure of hypertensive patients. The present communication confirms and enlarges the experience of these workers on the clinical and pharmacological effects of the dihydrogenated derivatives of ergotoxine in normal and hypertensive man.

**Materials and Methods.** The 3 compounds tested were dihydroergocornine (DHO 180), dihydroergokryptine (DHK 135) and dihydroergocristine (DCS 190). Fifteen patients received dihydroergocornine, 7 received dihydroergocristine, 8 were administered dihydroergokryptine, while 4 hospitalized patients received each of the 3 drugs at intervals of 3 or more days apart. The drugs were administered usually intravenously, and occasionally orally to hospitalized and ambulatory patients with hypertension, and also to normotensive subjects. The mean arterial pressure was calculated as half the sum of the systolic and diastolic

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blood pressure, which unless otherwise stated was taken with an arm cuff and mercury manometer. Control blood pressures were obtained for a period of  $1\frac{1}{2}$  hour prior to the administration of the drug.

**Results. Effect on Blood Pressure and Pulse Rate.** The hypotensive response to the administration of these dihydrogenated alkaloids of ergot was extremely variable in different patients (Table 1). All gradations of response occurred from insignificant to marked reductions in blood pressure. For example, after an intravenous injection of 0.5 mg. of dihydroergocornine in a

Following an intravenous injection of any of these compounds in a reactive subject the blood pressure usually fell progressively for 10 to 30 minutes to normotensive levels, and thereafter rose slowly to control values over a period of 1 to 24 hours or longer (Figure 1). Other subjects exhibited no reduction of arterial pressure or only slight hypotensive effects which lasted for 10 minutes or less. Similarly, the presence and the degree of postural hypotension varied in different individuals, but in general, was most marked in those who exhibited the greatest reduction of blood pressure in the supine position. Most commonly 5 to

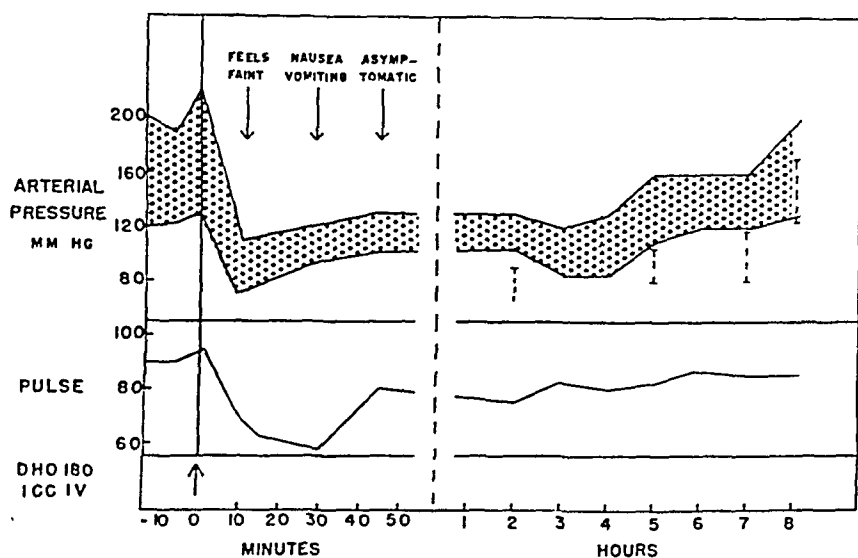


FIG. 1.—The typical response to the intravenous administration of 0.5 mg. (1 cc.) of dihydroergocornine (R. P., female, aged 23, with essential hypertension). The short vertical broken lines on the right half of the chart indicate blood pressure recordings made with the patient in the erect position.

reactive subject (Figure 1) the blood pressure decreased definitely within 1 minute and markedly within 10 minutes. During the early period after injection in such a patient, his pulse rate was unaffected and he had no symptoms, unless allowed to stand, whereupon he developed a further fall of blood pressure soon followed by bradycardia and collapse (Figures 1 and 2).

20 minutes following the administration of these drugs a reduction in cardiac rate occurred, sometimes accompanied by the side effects described below. A summary of the effects on blood pressure and pulse rate is given in Table I.

Of the available compounds studied, dihydroergocornine and dihydroergokryptine exhibited the greatest hypotensive activity (Tables 1 and 2). In

the supine position 8 of the 15 patients tested with dihydroergocornine exhibited a fall in blood pressure greater than 20 points systolic and 15 points diastolic, while 10 developed postural hypotension. The intravenous dose varied from 0.25 to 1.0 mg. When administered orally this dose produced little effect until it was increased to 4 to 8 mg. except in 2 patients, who responded

to as little as 2 mg. Following an oral dose of 8 to 10 mg., 5 of 7 patients developed a significant reduction in resting blood pressure, while 2 of these 5 also exhibited postural hypotension and collapse. In only 2 of the 5 patients was the reduction in blood pressure in the supine position as great after 10 mg. administered by mouth as it was after 0.5 mg. administered in-

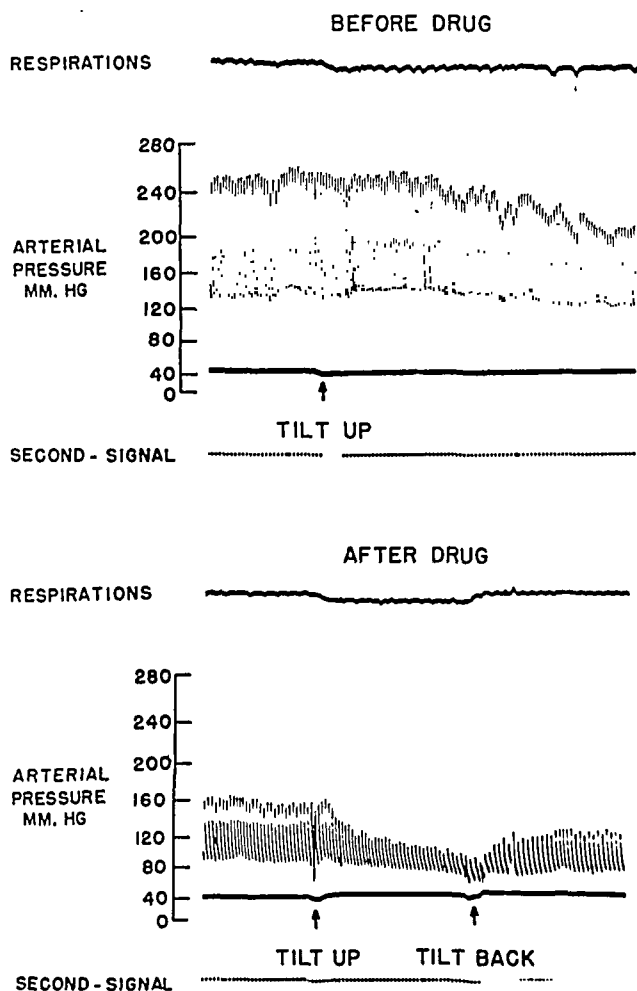


FIG. 2.—Postural hypotension, bradycardia and impending collapse (lower record) following the intravenous administration of 0.5 mg. of dihydroergocornine (K. M., female, aged 52). In the respiratory tracing inspiration is down. Arterial pressure was recorded from the brachial artery with a Hamilton manometer. The patient was lying on a table that at the arrow was tilted upright to an angle of 75°. Note that in the control period (upper record) she was able to stand for over a minute without the development of significant hypotension. After dihydroergocornine impending collapse occurred in 45 seconds following the tilt to the upright position.

TABLE 1.—SUMMARY OF THE EFFECTS OF THE 3 DIHYDROGENATED ALKALOIDS OF ERGOT ON THE BLOOD PRESSURE AND PULSE RATE AND THE INCIDENCE OF NAUSEA AND VOMITING

Drug	Number of Patients	Dose Intravenously Mgm.		Reduction in Mean Arterial Pressure Per Cent			Reduction in Pulse Rate Per Cent		No. of Patients Experiencing Side Effects	
		Mean	Range	Mean	Range	Standard Deviation	Mean	Range	Nausea	Vomiting
Dihydroergocornine . . . 15		0.5	0.25-1.0	18	0-41	12	16	0-33	4	2
Dihydroergocristine . . . 7		0.8	0.5-1.5	8	0-15	6	6	0-18	1	0
Dihydroergokryptine . . . 8		1.2	0.5-1.5	13	0-20	5	14	0-24	2	1

travenously. These data suggest, therefore, that to achieve a comparable effect by oral administration approximately 10 to 20 times the effective intra-

TABLE 2.—A COMPARISON OF THE HYPOTENSIVE EFFECT OF THE 3 DIHYDROGENATED ALKALOIDS OF ERGOT IN 4 PATIENTS WITH ESSENTIAL HYPERTENSION.

Patient	Drug	Dose Intravenously Mgm.	Reduction in Mean Arterial Pressure	
			%	
M.C.	Dihydroergocornine	0.5	28	
	Dihydroergocristine	1.5	15	
	Dihydroergokryptine	0.5	14	
M.G.	Dihydroergocornine	0.25	19	
	Dihydroergocristine	0.75	6	
	Dihydroergokryptine	1.5	11	
J.D.	Dihydroergocornine	0.5	5	
	Dihydroergocristine	0.5	3	
	Dihydroergokryptine	0.5	13	
M.N.	Dihydroergocornine	0.5	6	
	Dihydroergocristine	0.5	8	
	Dihydroergokryptine	0.5	8	

venous dose usually must be given. In addition to the hypotensive response, 4 of the 7 patients exhibited a reduction in pulse rate of from 10 to 20 beats per minute, and four developed nasal stuffiness. The hypotension, bradycardia and nasal stuffiness appeared 1 to 2 hours after the oral administration of the drug and lasted 1 to 12 hours.

**SIDE EFFECTS.** No serious toxic reactions were noted. Some degree of nasal stuffiness due to congestion of the nasal mucosa was present in almost every case. This could be successfully combated by the local application of 0.25% solution of aqueous neosynephrin. Visual accommodation was unimpaired. Nausea occurred in 7 of 30 patients

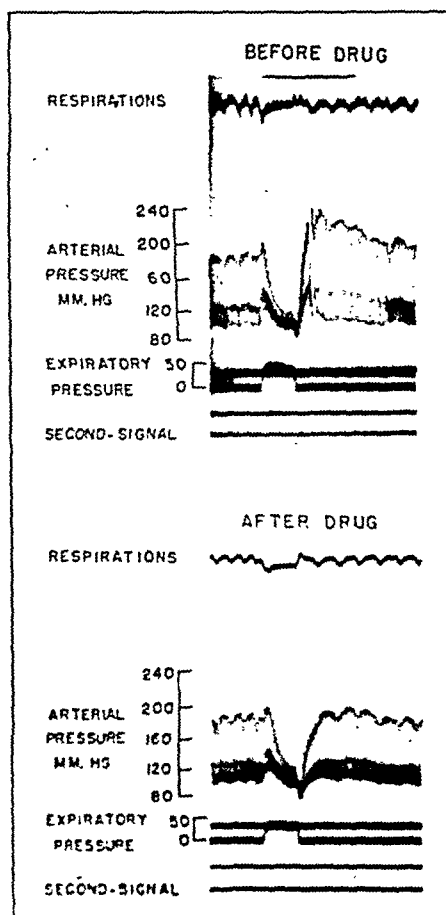


FIG. 3.—Inhibition of the hypertensive overshoot (lower record) following the Valsalva maneuver (R. S., female, aged 46, with essential hypertension). In the Valsalva maneuver the patient inspired deeply and exhaled for 10 seconds with maximal force against a fixed resistance. Other notations as in Fig. 2.

studied and in 3 of the 7 was followed by vomiting. These effects, often accompanied by sensations of faintness and giddiness, occurred during the period of bradycardia. It is worthy of note that the presence of side reactions was not related necessarily to the development of hypotension. For example, one patient exhibited a reduction of blood pressure from 245/128 to 150/80 with no side reactions of any kind except

response seen within the first few months after lumbodorsal splanchnicectomy or that observed after such drugs as sodium nitrite or tetraethylammonium bromide was not accompanied by a significant increase in pulse rate. Immediately after the patient assumed the erect position the blood pressure frequently was maintained for a brief period only to fall over the succeeding several minutes. Collapse began with

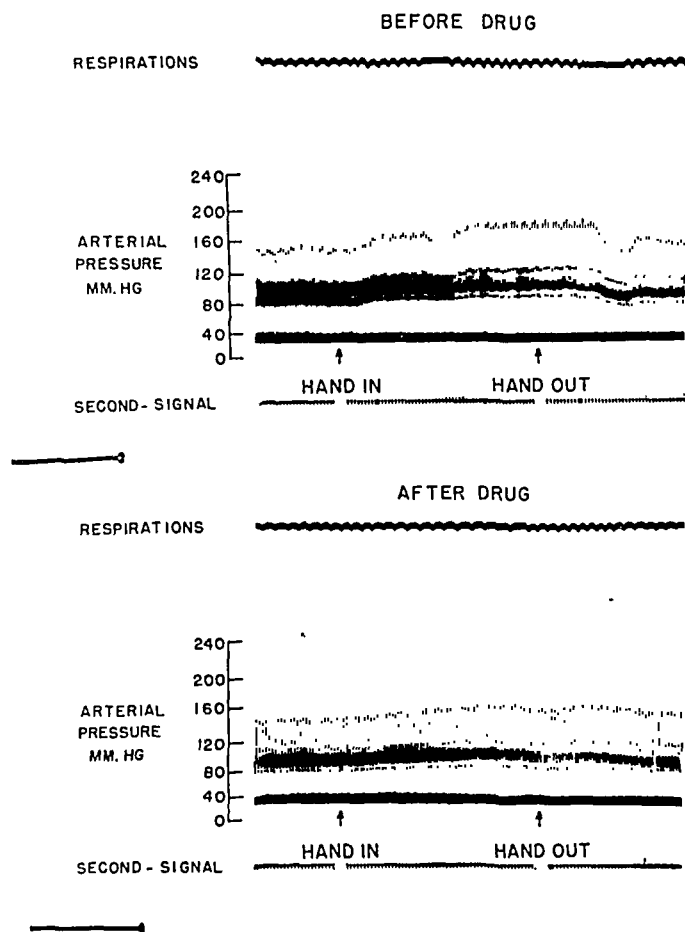


FIG. 4.—Inhibition of the cold pressor responses (C. T., male, aged 52, with essential hypertension following the intravenous injection of 0.5 mg. of dihydroergocornine). Other notations as in Fig. 2.

for the development of postural hypotension; while other patients without hypotension developed nausea and vomiting.

**MECHANISM OF ACTION.** The sympatholytic properties of these agents were demonstrated by the following effects.

(1) *The development of postural hypotension.* This, unlike the postural

yawning or nausea, followed by faintness, sweating, pallor and bradycardia. Postural hypotension occurred in normotensive as well as hypertensive individuals.

(2) *Diminution in vasopressor response to blood-pressure-lowering procedures.* After dihydroergocornine the hypertensive overshoots which normally occur after the Valsalva maneuver (Fig.

ure 3), and the tilt-back from the upright to the supine position<sup>14</sup>, were inhibited. This effect was identical with that observed after surgical splanchnicectomy<sup>14</sup> or the administration of certain other sympatholytic agents<sup>15</sup>.

(3) *Reduction of the cold pressor response* (Fig. 4).

(4) *Diminution of digital reflex vasoconstrictor responses both to "noxious" stimuli and to body cooling.* This

had no significant change in blood pressure. A similar inhibition of these reflexes was also observed in several normotensive individuals following the administration of dihydroergocornine.

(5) *A reduced hypotensive response to the drug in the same patient studied after as compared with before lumbo-dorsal splanchnicectomy.* Thus, the same dose in 3 patients produced an average reduction of 6% of mean arte-

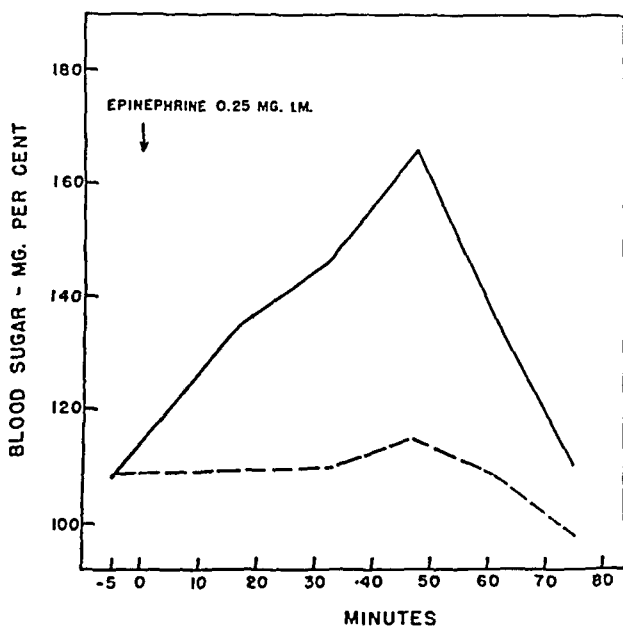


FIG. 5.—The blocking of hyperglycemic response to the intramuscular injection of 0.25 mgm. of epinephrine (J. S., male, aged 32, with a diagnosis of latent syphilis under treatment with penicillin). Normal diet; tests carried out in the postabsorptive basal state. In the 2d test, 2 days following the control test, 15 minutes prior to the injection of epinephrine, 1.0 mg. of dihydroergokryptine was administered intravenously, and immediately following the injection of adrenalin an additional 0.5 mg. of dihydroergokryptine was given by the same route. Another such test on a different patient gave similar results.

effect measured by digital plethysmography<sup>3</sup> and/or cutaneous thermometry<sup>12</sup> varied in amount from slight to almost complete suppression of sympathetic reflex vasoconstrictions in the fingers and toes. However, it bore no relation to the degree of hypotension. Thus, the reflex vasoconstrictions were only slightly inhibited in two hypertensive patients who exhibited marked reductions of resting arterial pressure, while they were almost completely abolished in two other patients who

had no significant change in blood pressure after lumbodorsal splanchnicectomy as compared to a 14% reduction prior to operation. By contrast, the drug produced the same degree of slowing of cardiac rate before and after lumbodorsal splanchnicectomy. Further, the tachycardia which otherwise occurred in the erect position after splanchnicectomy was inhibited by the administration of dihydroergocornine.

The adrenolytic properties of dihydroergokryptine were clearly shown by the inhibition in 2 subjects of the hy-

perglycemic response to the injection of epinephrine (Figure 5). The inhibition of the pressor response to epinephrine was less readily demonstrated. However, by using doses of from 1.0 to 1.5 mg. of dihydroergokryptine and by administering a minimal effective dose of epinephrine by constant intravenous drip in dilute solution, an adrenolytic effect on the blood pressure response could be demonstrated. Occasionally there was also inhibition of the tachycardia and mydriasis which ordinarily follows the injection of epinephrine.

In addition to the sympatholytic and adrenolytic actions noted above after any of these agents there were evidences of vagotonic effects including nausea, vomiting and bradycardia. These effects may have been due to unopposed vagal action rather than to direct vagal stimulation. The bradycardia, but not the hypotension, could be abolished by atropine. In contrast to the early appearance of signs of sympathetic inhibition, evidences of vagal stimulation were usually delayed until 10 to 20 minutes after the intravenous injection of the drug.

Dihydroergocornine apparently increased the tendency to collapse from venous pooling. Following administration of the drug postural hypotension and collapse were frequent, but could be prevented by the application of a tight abdominal binder and elastic stockings. Similarly collapse often was produced in the supine position after DHO 180 by the inflation of venous congesting cuffs high on the extremities for several minutes, when it could not be so produced before the drug.

**Discussion.** Although these dihydrogenated derivatives of ergot bear certain resemblances to other sympatholytic agents, their action is not identical with any of them. For example, in animals the ergot alkaloids have been shown to produce a central blockade of sympathetic reflexes<sup>11</sup>. This effect

as well as the absence of significant tachycardia during the period of postural hypotension resembles that of pamaquine and pentaquine.<sup>6,8,10</sup> The ergot alkaloids differ from these latter agents, however, in that they also exhibit adrenolytic properties.

The selective adrenolytic, sympatholytic and vagotonic properties of the dihydrogenated ergotoxine compounds are in marked contrast to the indiscriminate blockade of all autonomic ganglia produced by the tetraethylammonium salts.<sup>1</sup> On the other hand their adrenolytic and sympatholytic properties suggest a similarity of action to that of dibenamine<sup>9</sup> and to Fourneau compound 883F<sup>5</sup>. However, the available evidence indicates that dihydroergocornine acts centrally<sup>11</sup> whereas dibenamine and Fourneau compound 883F are said to act peripherally.

One of the most striking features of dihydroergocornine in therapeutic doses was the marked variability of its hypotensive effect in different individuals. Its hypotensive action appeared to be related more to individual susceptibility than to size of dose as based on height, weight or age. Thus, increasing the dosage did not enhance the hypotension in certain patients who showed a poor response to standard amounts of the drug. The variability of action applied not only to the hypotension, but also to the other sympatholytic effects. Similar variability has been noted with other sympatholytic agents such as pentaquine<sup>6</sup> and tetraethylammonium bromide<sup>7</sup>.

Bluntschli and Goetz<sup>2</sup> observed that parenteral doses of 0.1 to 0.3 mg. of dihydroergocornine had a greater hypotensive effect and a lesser incidence of side reactions than the larger dose of 0.5 mg. used in most of the cases in the present study. Increasing the dose beyond 0.5 mg. did not increase the hypotensive response in our series, whereas it did increase the incidence of side



effects. The question of dosage required to obtain optimum therapeutic (hypotensive) effects with minimum side reactions requires further investigation.

The search for compounds to produce a "chemical sympathectomy" as yet has not yielded a drug of practical therapeutic value in the treatment of patients with essential hypertension. Such an agent should be nontoxic in therapeutic doses; it should have a sufficiently long duration of action so that the patient may obtain his sleep, and ideally, it should be effective by mouth. In several respects dihydroergocornine fulfills these criteria. It is relatively nontoxic in therapeutic doses, and in selected cases, it reduces blood pressure in sufficient magnitude and duration to warrant additional clinical trial. However, in most patients the effective oral dose is so large that, for the present, this route of administration is neither practical nor economically feasible. The most serious limitations to its clinical use are the development of side reactions in some patients and the absence of significant hypotensive effects in others. In addition, the production of postural hypotension, which the drug has in common with all other sympatholytic agents, imposes a hardship on the patient. Definitive evaluation of its clinical usefulness must await long term studies in selected cases who exhibit a satisfactory hypotensive response to oral administration. The possibility of using dihydroergocornine as a test agent in predicting the outcome of splanchnicectomy is under investigation at present.

**Summary and Conclusions.** 1. Three new dihydrogenated alkaloids of ergot have been found to lower the blood

pressure of a significant percentage of hypertensive patients following intravenous injection. The most effective agents in the group were dihydroergocornine and dihydroergokryptine. The degree and duration of hypotensive activity were extremely variable in different subjects.

2. These drugs have been shown to exert sympatholytic, adrenolytic and vagotonic properties:

a) Sympatholytic actions included the production of postural hypotension, the inhibition of hypertensive overshoots following depressor stimuli, diminution of reflex sympathetic vasoconstriction in the digits, and moderation of the cold pressor response. In addition the drug had a reduced hypotensive action following lumbodorsal splanchnicectomy.

b) Adrenolytic activity of dihydroergokryptine was demonstrated by inhibition of the hyperglycemic response to epinephrine, and under proper experimental conditions diminution of the pressor response, tachycardia and mydriasis, following epinephrine.

c) Evidence of vagal stimulation or of unopposed vagal activity was manifested by bradycardia and in some cases by nausea and vomiting.

3. No serious toxic reactions were observed. Nasal stuffiness occurred in almost every case. With the dosage used the other side effects, notably nausea, vomiting and faintness occurred in approximately 25% of the patients tested.

4. In selected cases dihydroergocornine was effective by the oral route usually in doses approximately 10 to 20 times greater than the effective intravenous dose.

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# THE IMMEDIATE SEQUELÆ OF MYOCARDIAL INFARCTION THEIR RELATION TO THE PROGNOSIS

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IN spite of the marked upsurge of optimism in the evaluation of coronary artery disease, myocardial infarction remains one of the most unpredictable entities in clinical medicine. The reason for this is the multiplicity of factors influencing its course and immediate prognosis, for in addition to the actual derangement of the circulation caused by myocardial infarction, the course of the disease is often altered by secondary complications.

The immediate prognosis of acute myocardial infarction depends largely on the myocardial necrosis and its sequelæ. Coronary artery disease is the usual initiating factor in obstructing the blood flow to a portion of the myocardium, but once heart muscle necrosis has developed the damage to the myocardium affects the course of the disease, regardless of whether or not there is progression of coronary arteriosclerosis.

In physiologic terms, the immediate effect of acute myocardial infarction is failure of the left ventricle, the muscle of which almost always is the site of the myomalacia.<sup>1,4,6,8</sup> It is, however, clear to all observers that progressive cardiac failure is not apparent clinically in all cases, not even in all fatal ones. The frequency of other secondary factors causing death indicates that the heart is not necessarily damaged beyond repair in those who die from myocardial infarction. The purpose of this study is to investigate the immediate sequelæ of myocardial infarction and their influence upon the mortality from it, in patients who were observed clinically and examined post-mortem, with a special effort to separate cases in which death was due to irrepar-

able cardiac damage from those in which the cause of death was a secondary complication.

**Material and Methods.** The study is based on 130 consecutive cases of recent infarction of the myocardium found on gross examination in the routine autopsy material of the Department of Pathology during the 8 year period of 1937 to 1944. Doubtful cases were eliminated, and so were cases in which clinical records were inadequate for the study. No special methods of visualization of the coronary tree postmortem were used, but the coronary arteries were carefully examined and the myocardium searched, and both were studied microscopically. Clinical records were examined and particular attention was paid to the course of illness, circumstances preceding death and the mode of death.

Special care was exercised in evaluation of the patient's condition before the development of myocardial infarction, in order to separate patients who already were ill at that time. The decision as to what constitutes the immediate cause of death was reached in each case after a most careful consideration of clinical data and the autopsy findings. In cases with multiple complications one factor was selected which was thought to have had a decisive effect on the course of the disease.

In addition to the course and cause of death, pathologic evidence of damage to the heart was studied, particularly the size of the infarction, the presence of myocardial scars and of cardiac hypertrophy. Infarcts were classified according to the size as "large" and "small," and only definite myocardial scars were accepted as evidence of previous infarction, usually with a corresponding old coronary occlusion. Hearts were classified as hypertrophied if the weight exceeded 500 gm.

**Findings. GENERAL CONSIDERATIONS.** Gross pathologic descriptions of the 130 cases showed that the recent infarcts of the myocardium were diagnosed as massive in 36 cases, while in the remaining 94 cases their sizes varied from 1 to 8 cm. in diameter. Infarcts were caused by coronary arteriosclerosis in 126 cases, by coronary embolism in 3, and by periarteritis nodosa in 1. In the arteriosclerotic group, coronary thrombosis was demonstrated in 102 cases, and occurred in 1 branch in 82, and in 2 branches in 20 cases. Coronary arteriosclerosis of the branches supplying the non-infarcted myocardium was described as severe in 65 cases, moderate in 35 and mild in 26 cases. Mural thrombosis was found in 78 cases (60%).

A review of the clinical data revealed that the patients fell into 2 main categories: those in whom myocardial infarction developed as a complication of a pre-existing serious illness, and those in whom infarction was in the clinical sense a primary illness. Thirty-five patients fell into the former category; 22 of them suffered from cardiac failure prior to the development of myocardial infarction and 13 suffered from non-cardiac conditions such as periarteritis nodosa, septicemia, uremia, diabetic acidosis, lobar pneumonia, cancer, lung abscess, empyema, or had myocardial infarction after a major surgical operation. In these patients the pathologic findings in the coronary arteries and the myocardium were comparable to the remainder of the series, yet, from the clinical standpoint they were thought to be unsuitable for the study of the effect of myocardial infarction upon the circulation. In patients who were seriously ill before the development of the infarction even slight damage to the myocardium may become the immediate cause of death, and myocardial infarction is a mere terminal event, comparable to bronchopneumonia. It was decided, therefore, to eliminate from the clinical-pathologic correlation these 35 cases and limit the material to the 95 cases of "primary"

myocardial infarction; that is, patients who prior to the infarction had little limitation of activities, belonging to the functional Classes I and II (classification of the American Heart Association).

**"PRIMARY" MYOCARDIAL INFARCTION.** The 95 cases of "primary" myocardial infarction were divided in 4 groups, according to the cause of death and clinical course. Group 1 included those who developed progressive circulatory failure, either congestive failure or shock, and who at autopsy did not show any important complications. There were 28 patients in this group. Group 2 consisted of 24 patients who died suddenly, but showed at necropsy no immediate cause of death other than the infarction, suggesting that death was in them due to a fatal arrhythmia. In 12 patients of this group some observations as to the mode of death were available, the remainder were found dead, or died without warning. Six patients died during various activities (walking, trying to get out of bed, straining on the bed-pan, etc.). One patient developed symptoms suggesting acute pulmonary edema and died before treatment could be started; 4 patients had attacks of anginal pain immediately preceding sudden death; 3 had convulsions. In this group at least 24 hours elapsed between the onset of the infarction and the sudden death.

Group 3 included 32 patients who died as a result of complications demonstrable at autopsy. In all patients included in this group the clinical course, mode of death and autopsy findings suggested that the complications turned the tide of a case from a possible recovery, or at least accelerated death. The following complications were found: rupture of the infarcted left ventricle was present in 8 cases (in 7 of them into the pericardium and in the eighth through the interventricular septum into the right ventricle), embolic phenomena were found in 15 cases, including cerebral embolism in 6, massive pulmonary embolism in 5, embolism to extremities in 3, and mesenteric embolism

TABLE 1.—RELATIONSHIP BETWEEN THE IMMEDIATE CAUSES OF DEATH AND THE VARIOUS TYPES OF CARDIAC DAMAGE FOUND AT AUTOPSY IN PRIMARY MYOCARDIAL INFARCTION

(Group 1: Progressive Circulatory Failure. Group 2: Sudden Death. Group 3: Death Due to Complications. Group 4: Other Causes of Death)

	Group 1	Group 2	Group 3	Group 4
Massive myocardial infarction . . . . .	10	7	15	2
Old and recent infarction . . . . .	8	7	2	4
Myocardial infarction and cardiac hypertrophy . . . . .	6	3	7	3
Other cases of myocardial infarction . . . . .	4	7	8	2
Total . . . . .	28 (30%)	24 (25%)	32 (34%)	11 (11%)

TABLE 2.—RELATIONSHIP BETWEEN THE CONDITION OF PATIENTS WITH PRIMARY MYOCARDIAL INFARCTION AND VARIOUS TYPES OF CARDIAC DAMAGE FOUND AT AUTOPSY

	Patients in serious condition	Patients in good condition
Massive myocardial infarction . . . . .	17	17
Old and recent infarction . . . . .	12	9
Myocardial infarction and cardiac hypertrophy . . . . .	8	11
Other causes of myocardial infarction . . . . .	12	9
Total . . . . .	49	46

TABLE 3.—DEGREE OF CORONARY ARTERIOSCLEROSIS IN VARIOUS CLINICAL GROUPS OF PRIMARY MYOCARDIAL INFARCTION\*

Coronary Arteriosclerosis	Group 1	Group 2	Group 3	Group 4	Total
Mild . . . . .	7	5	9	2	23
Moderate . . . . .	6	6	13	1	26
Severe . . . . .	15	13	10	8	46

\* See Table 1.

TABLE 4.—TIME INTERVAL BETWEEN THE ONSET AND DEATH FROM MYOCARDIAL INFARCTION AND ITS RELATIONSHIP TO THE CAUSE OF DEATH

No. of days between initial attack and death	Group 1	Group 2	Group 3	Group 4	Total
1-3 . . . . .	8	7	2	1	18
4-7 . . . . .	7	10	10	1	28
8-10 . . . . .	4	2	3	2	11
11-14 . . . . .	7	1	3	3	14
15-21 . . . . .	1	3	9	2	15
22-30 . . . . .	..	1	5	..	6
Over 30 . . . . .	1	..	..	2	3

in 1. Other complications, not directly connected with the infarction, were: lobar pneumonia (appearing after the infarction) in 2, empyema, diabetic acidosis, uremia, gastro-intestinal hemorrhage, unexplained ileus in 1 each. Two patients died following a surgical operation for an intercurrent condition. In 20 of the 32 cases in this group the patients were progressing satisfactorily up to the time of development of the complication, while in 12 they were in serious condition and in them complications presumably only accelerated an inevitable fatal outcome. It is of interest to note that 4 of the

5 patients with massive pulmonary embolism occurred in seriously ill patients.

Group 4 consists of miscellaneous cases, which did not fit into any of the first 3 groups. Five patients died of recurrent coronary occlusion while in the hospital for the treatment of myocardial infarction: 2 of them during the 1st and 3 in the 2nd week after the first attack. Four patients had a prolonged course with repeated remissions and exacerbations, for which no explanation was apparent. Two patients died under circumstances suggesting digitalis toxicity.

A relationship between the extent of

TABLE 5.—RELATIONSHIP BETWEEN AGE AND CAUSE OF DEATH IN PRIMARY MYOCARDIAL INFARCTION

Age (yrs.)	Group 1	Group 2	Group 3	Group 4	Total
Below 50 . . . . .	5	7	4	1	17
51-70 . . . . .	17	14	20	8	59
Over 70 . . . . .	6	3	8	2	19

TABLE 6.—RELATIONSHIP BETWEEN SHOCK AND CAUSE OF DEATH IN PRIMARY MYOCARDIAL INFARCTION

	Group 1	Group 2	Group 3	Group 4	Total
Patients in severe shock . . . . .	5	..	2	..	7
Patients in mild shock . . . . .	9	1	1	2	13
Totals:	—	—	—	—	—
Patients in shock . . . . .	14	1	3	2	20
Patients without shock . . . . .	14	23	29	9	75

TABLE 7.—RELATIONSHIP BETWEEN LEFT VENTRICULAR FAILURE AND CAUSE OF DEATH IN PRIMARY MYOCARDIAL INFARCTION

	Group 1	Group 2	Group 3	Group 4	Total
Patients with severe left ventricular failure . . . . .	6	1	3	..	10
Patients with mild left ventricular failure . . . . .	17	11	19	8	55
Totals:	—	—	—	—	—
Patients with left ventricular failure . . . . .	23	13	22	8	65
Patients without left ventricular failure . . . . .	5	12	10	3	30

TABLE 8.—RELATIONSHIP BETWEEN RIGHT VENTRICULAR FAILURE AND CAUSE OF DEATH IN PRIMARY MYOCARDIAL INFARCTION

	Group 1	Group 2	Group 3	Group 4	Total
Right ventricular failure . . . . .	3	1	11	2	17
% of total number of patients in the group . . . . .	10%	4%	34%	18%	18%

myocardial damage as recorded at autopsy and the immediate cause of death is presented in Table 1. Table 2 shows these same pathologic data correlated with the patient's condition, regardless of the cause of death. In this table the first column represents roughly patients whose chances of recovery from acute myocardial infarction appeared slight, and the second column those who had a good prospect for survival of the attack. The comparable incidence of the various pathologic findings believed to show the extent of myocardial damage in the 2 groups indicates a lack of correlation between the seriousness of the clinical course and the extent of myocardial damage.

Table 3 shows the degree of coronary arteriosclerosis with particular reference to the non-occluded vessels in the 4 clinical groups. There is a somewhat lower incidence of severe arteriosclerosis of the coronary arteries in patients who died of secondary complications.

Table 4 shows the time of death in to the cause of death. It shows

that the time between the development of myocardial infarction and death was shorter in patients who died of circulatory failure and of fatal arrhythmia than in those who developed secondary complications. The time of death from the important complications was as follows: rupture of the heart occurred within the 1st week in 4 cases, in the 2nd week in 2, and in the 3rd week in 2. Death from embolic phenomena occurred in 5 cases in the 1st week, in 5 in the 2nd week, and in 4 in the 3rd week.

Table 5 presents the relationship between the age of the patients and the causes of death. There was a slightly higher incidence of fatal arrhythmias in younger patients; otherwise there were no striking differences in the mode of death in various age groups.

The remaining 3 tables present the incidence of various forms of circulatory failure in the 4 groups of patients. Shock (Table 6) was observed in 20 cases (21%), 14 of which occurred in Group 1, accounting for half of this group. All patients

with shock, with 1 exception, died within the first 8 days after the initial attack.

Left ventricular failure (Table 7) was noted in 65 patients (68%) and showed highest incidence in Group 1, both in frequency and severity.

Right ventricular failure (Table 8) was recorded in 17 cases (18%). There were fewer cases of right ventricular failure in Group 1, and it appeared most frequently in patients who died from secondary complications (11 cases). It was noted that in 7 of these 11 cases pulmonary complications were present, namely infarctions in 5 and pneumonia in 2.

**Discussion.** Patients with fatal myocardial infarction can be divided roughly into 3 types: (1) those who die within minutes or hours after the onset of coronary occlusion; (2) those who survive the initial attack, but fail to develop adequate circulatory adjustment; (3) those who show effective compensatory measures but die from secondary causes. Only the last 2 types of patients were studied here: patients with immediately fatal coronary occlusion do not live long enough to reach the hospital, and therefore were not encountered in this material. Of the 95 patients with "primary" myocardial infarction, 49 showed clinical evidence of circulatory failure; 19 died in shock, 14 in severe congestive failure without complications, and 16 had cardiac failure but died of intercurrent complications.

These 30 patients who were in severe cardiac failure and possibly the 19 patients in shock constitute cases in which the myocardium was apparently damaged beyond repair. It is shown that the incidence of massive infarcts, of old myocardial scars, and of cardiac hypertrophy in these patients is the same as in fully compensated cases. This suggests that there is no correlation between the extent of gross damage to the heart muscle and the functional capacity of the myocardium. It would perhaps be unjustified to accept unequivocally on the basis of relatively small series of cases a far-reaching conclusion, that

the degree of myocardial damage does not influence the course of myocardial infarction. It is safer to interpret these findings as a mere illustration of the fact that under favorable conditions patients may develop very large infarcts, or infarcts in hearts previously damaged by heart disease, and yet show enough compensatory measures in the circulatory system to render them free from clinical signs of circulatory failure.

It appears then that the most crucial period of time in an attack of coronary occlusion is the first few moments after the onset. In most severe cases patients may not even live long enough to develop recognizable myocardial necrosis. Those patients who survive the critical first few hours apparently have effective compensatory factors working in their favor. At this stage the various secondary complications of myocardial infarction become more menacing to the patients than the derangement of the circulation.

Of the various types of circulatory insufficiency, left ventricular failure is the commonest, but the least serious of all sequelæ of myocardial infarction. In this report only fully developed left ventricular failure was recorded, but it has previously been demonstrated that latent, or mild left ventricular failure can be shown in almost every case of myocardial infarction.<sup>5</sup>

In contrast, right ventricular insufficiency occurs infrequently in the course of myocardial infarction, but is very serious, almost invariably fatal. It is shown that right-sided cardiac insufficiency is rare in patients who run the course of progressive circulatory failure, and occurs more often in association with pulmonary infarction or infection. It is likely that the changes in the pulmonary circulation due to these complications contribute to the overloading of the right heart. If confirmed, this relationship may be of some diagnostic value by directing attention to the possibility of pulmonary complications in cases where right ventricular failure develops prominently

in the course of myocardial infarction.

Persistent shock was present in 20 % of patients and was in all of them the main or contributory immediate cause of death. The present-day inadequate knowledge of the pathogenesis of shock in myocardial infarction does not permit a definite statement, as to whether shock is entirely due to myocardial insufficiency, or in part, to peripheral circulatory failure. It is therefore not known whether it should be considered as evidence of irreversible damage to the myocardium, or a complicating factor, which, perhaps, could be favorably influenced by treatment.

Sudden death responsible for 25 % of fatalities in this series is the most serious consequence of myocardial infarction. The mechanism of death in such cases is usually attributed to ventricular fibrillation, although only in the rarest cases is actual proof of this arrhythmia available. Indirect evidence is based on animal experiments<sup>9</sup> and on the high incidence of milder forms of arrhythmia preceding sudden death in patients with myocardial infarction. This has not been confirmed in the present series. It should also be pointed out that Weiss<sup>7</sup> emphasized the importance of other mechanisms of sudden death, related to overactive cardio-inhibitory reflexes. The few observations as to events immediately preceding sudden death in this series suggests that the mechanism may be different in various cases. It is also noteworthy that sudden death was in a number of patients precipitated by activity.

The importance of thrombo-embolic phenomena<sup>2,3</sup> as a fatal complication of myocardial infarction is fully confirmed in this series: 21 % of patients died as a result of them, and 60 % of cases had mural thrombi in the endocardium.

Finally, cardiac rupture is a small but definite hazard of acute myocardial infarction. The incidence of cardiac perforation in this series is comparable to that of other investigations.

The most important point brought out in this report is the fact that at least 50 %

of the patients who died during the acute stage of myocardial infarction had evidence of effective compensatory measures in the circulation and died because of secondary complications. This figure represents the most conservative estimate, for all patients in persistent shock and severe cardiac failure were assumed as representing irreversible cardiac damage, without consideration of the possibility that different therapy might have prevented a fatal outcome in some of them. It appears, then, that from the standpoint of pathologic changes and functional capacity of the myocardium, death is preventable in a large proportion of patients who survive the initial attack of pain of myocardial infarction. All patients in this series underwent standard treatment for myocardial infarction, and it is obvious that more effective means of prevention of secondary complications are needed if the mortality from myocardial infarction is ever to reach the irreducible minimum. The recent introduction of anticoagulants in the treatment of myocardial infarction<sup>10</sup> is a step in the right direction, but sequelæ of myocardial infarction other than thrombo-embolic phenomena are in need of investigation from the standpoint of prevention and treatment.

**Summary and Conclusions.** 1. A series of 130 unselected cases of recent myocardial infarction found at autopsy was examined. In 35 patients myocardial infarction was a terminal event in otherwise seriously ill patients and was regarded as of little clinical interest. The remaining 95 patients were apparently well prior to the onset of the myocardial infarction and were subjected to detailed analysis as "primary" myocardial infarction.

2. The immediate cause of death in this group of 95 cases was: progressive circulatory failure, with or without shock, in 28 cases; sudden death due to arrhythmia in 24 cases; embolic phenomena in 15 cases; cardiac rupture in 8 cases; secondary coronary thrombosis in 5 cases. In the



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remaining 15 cases death was due to incidental complications not related to myocardial infarction.

3. No significant correlation was found between the age of the patients, the degree of the coronary arteriosclerosis, the size of the infarction and the presence of myocardial scars and of cardiac hypertrophy on one hand, and the course, the duration of illness, and the frequency of complications on the other hand. This is interpreted as indicating the adequacy of circulatory adjustment even in cases with extensive damage to the heart.

4. The prognosis of acute myocardial infarction is unpredictable because the importance of cardiac insufficiency—the direct consequence of the damage to the myocardium—is outweighed by secondary complications. The immediate mortality is twice, or perhaps 3 times greater than the estimated number of cases with irreparable cardiac damage. The important sequelæ of myocardial infarction, which can be considered potentially preventable causes of death, are: serious arrhythmia, thrombo-embolic phenomena and shock.

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# DIGITOXIN POISONING

REPORT OF 30 CASES

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Modern digitalis is a very potent drug. Like its predecessors, since the time of Withering, it has well known symptoms and signs of overdosage, intoxication, or poisoning. Using ordinary doses and with ordinary care, the physician rarely has to contend with the problem of digitalis poisoning. Therefore, when he turns to and uses the most potent of all *Digitalis purpurea* glucosides, digitoxin, in the recommended dosage, and despite care he frequently encounters the symptoms and signs (mainly) of digitalis overdosage, it is a problem that requires serious consideration.

During the period from January 1, 1947, to January 30, 1948, I had the unusual experience of seeing 30 patients with digitoxin poisoning. None of the patients had received digitalis in any form previous to the administration of the oral digitoxin in the recommended dosage. All of the physicians who treated these patients stated that the advised method and dosage for giving this digitalis glucoside were used, and that the alarming signs appeared early, from the 2nd to the 10th day, rather than late. Electrocardiograms were available in all instances, previous to, during, and after all the toxic manifestations had completely disappeared.

Serious toxic manifestations seem to have been more frequently observed from the use of the digitalis glucosides than from the whole-leaf preparations.<sup>7</sup> Since all my own work has been with

the whole-leaf digitalis preparations<sup>4</sup> I may seem to be prejudiced in their favor. However, it seems clear that most of the difficulties encountered due to digitalis therapy result from the use of the isolated glucosides. The incidence of digitalis poisoning has risen in direct relation to the increased use of these glucosides.<sup>7</sup>

Over a period of 15 years, the last 8 associated with a large medical service at the Cook County Hospital (the Ward 61 service of Dr. Harry J. Isaacs), the writer has encountered digitalis poisoning infrequently. If one such case was seen a year, it was considered a "find" for teaching purposes. Most often it was present in a patient with long-standing decompensated rheumatic heart disease: mitral stenosis, insufficiency, and auricular fibrillation, and who would show a bigeminy with long, continued digitalis therapy. Considering the large number of cardiac patients seen and the length of time treated, the margin of safety with the whole-leaf digitalis preparations must be very great to account for the infrequency of symptoms and signs of overdosage. Until late in 1946 the common symptoms and signs of digitalis overdosage which I saw were anorexia, nausea and vomiting, occasionally with, but most often without, bigeminy, or a marked sinus bradycardia without symptoms. I had yet to see auricular fibrillation, auriculo-ventricular block, partial heartblock, sinus arrest, and paroxysmal ventricular

tachycardia as manifestations of digitalis poisoning. Late in 1946 and early in 1947, when many switched to the isolated digitalis glucoside preparations, cases of digitoxin poisoning began to appear.

**Age, Sex and Color.** A total of 30 such patients have been seen in 13 months. Their clinical data are the subject of this report. There were 17 (56%) females and 13 (44%) males, all white, whose ages varied from 21 to 72 years. The average age was 55 years. All were educated, intelligent individuals, with whom there had been no difficulty in either understanding the instructions or in the taking of the prescribed digitoxin preparations. In the series of 44 cases reported by Herrmann *et al.*,<sup>7</sup> 25 were Negro patients, so that

of the cardiac mechanism, as 20 (66.6%) had no symptoms of digitoxin poisoning. The other 10 complained of anorexia, nausea, vomiting, weakness and fatigue, symptoms which had not been present previous to the digitoxin administration. No instances of diarrhea, yellow vision, or scotoma were seen. All the patients had regular rhythm at the time congestive failure occurred and when the administration of digitoxin was started. In the 44 cases reported by Herrmann and his associates,<sup>7</sup> the most common disorder of cardiac action was paroxysmal tachycardia with auriculoventricular block (20 cases). Among my 30 cases, the 2 chief findings were premature contractions and auricular fibrillation (Table 1). Bigeminy,<sup>8</sup> the clinical sign

TABLE 1.  
Electrocardiographic Signs in 30 Cases of Digitoxin Poisoning

Premature Contractions .....	11
Irregular .....	5
Bigeminy .....	6
Auricular Fibrillation .....	10
Auriculoventricular Block .....	5
S-T and T depressed .....	19
Alone .....	6
Sinus Bradycardia .....	4
Partial Heart-Block (P-R prolonged beyond 0.24 sec.) .....	4
Sinus Arrest (Dropped Beats) .....	2
Paroxysmal Ventricular Tachycardia .....	1

the authors felt that this might account for failure to understand or observe directions.

**Types of Heart Disease.** The types of heart disease associated with the congestive heart failure, for which the digitoxin had been given, were not significant. There were 7 with rheumatic heart disease, 7 hypertensives, 7 hypertensive-coronary cases and 1 with no heart disease. The hypertensives, either alone or in combination with arteriosclerotic (coronary) heart disease, were most common, as has been shown previously.<sup>3</sup>

**Symptoms and Signs.** Those noted in the 30 patients were mainly disorders

most often associated with overdigitalization, was noted in 6 (20%) of the 30 patients. S-T and T wave depression, the electrocardiographic sign most frequently seen with digitalis overdose, was found in 19 cases, but this was the sole graphic abnormality in only 6 of the 19.

Only 2 deaths occurred among the 30 patients, 1 due to paroxysmal ventricular tachycardia and the other with auricular fibrillation and bigeminy. The low mortality was due to the awareness of the physicians treating these patients, but some of the doctors were greatly surprised, and chagrined, that such serious cardiac disorders oc-

curred without symptoms on the usual advised dosage of the digitoxin preparations.

**Discussion.** Although this report presents only 30 instances of digitoxin poisoning, it may serve to emphasize certain points. All of the patients were treated by the so-called latest development in digitalis therapy (yet digitoxin was first described as long ago as in 1869 by Nativelle).<sup>9</sup> The potency of digitoxin orally administered is approximately 1000 times that of U.S.P. digitalis leaf; 0.1 mg. digitoxin is equivalent to 0.1 gm. (gr. iss) whole-leaf digitalis and to 1 U.S.P. XII Digitalis Unit. Warnings were issued<sup>6,2,4c</sup> on U.S.P. XI Digitalis, which became U.S.P. XII in most instances, that the potency of digitalis was increased clinically about 50%. Many pharmaceutical manufacturers then advised a maintenance dose of whole-leaf digitalis of about gr.  $\frac{3}{4}$ . Now when these same pharmaceutical houses offer and promote very vigorously a 0.1 mg. tablet of digitoxin, considered as equivalent to 1 U.S.P. XII Digitalis Unit (which in turn ranges anywhere from gr. ss to gr. iss depending on the source, purity, and standardization of each whole-leaf preparation) the confusion becomes greater than ever. Even by adhering to all the directions and instructions issued with the digitoxin preparations, one is still not able to avoid intoxication and poisoning.

Digitoxin also has a peculiar action on the sinus rate. Braun and Wosika,<sup>3</sup> quoting Oettel, emphasized the so-called "paradoxical action" of the digitalis glucosides (an increase in the sinus rate and the appearance of ectopic beats). Most recently, Stone<sup>10</sup> reported a case of auricular tachycardia and auriculo-ventricular dissociation following 1.2 mg. of digitoxin (orally) in one dose, a combination which I have not encountered to date. In his patient, a man weighing 125 pounds, 1.2 mg. of digitoxin was considered excessive

as the initial oral digitalizing dose. When part of the 1.2 mg. was eliminated the auricular tachycardia and A-V dissociation disappeared, but there was still evidence of toxicity in the prolongation of the P-R interval to 0.28 sec. Because of the high percentage of toxicity in their cases, Batterman and De Graff<sup>1</sup> recommended that digitoxin be made available in 0.05 mg. tablets. Since the recommended oral dose is 1.2 to 1.5 mg. at intervals of 4 to 6 hours, followed by a daily maintenance dose of 0.1 to 0.2 mg., their excellent suggestion would make possible the halving of the dosage.

From such experience it would seem that considerable caution needs to be used in the treatment of patients with congestive heart failure with the digitoxin preparations. Purified glucosides will not result in a more efficient or safer digitalization.<sup>1</sup> It might be safest to use a good whole-leaf preparation of *Digitalis purpurea* or *lanata*, since it has been shown to be the drug of choice for routine use.<sup>11</sup> It may be old-fashioned, but it certainly has a much greater factor of safety. At least the warning symptoms and signs of whole-leaf digitalis overdosage, infrequently as they occur, are easily recognized clinically.

Whenever digitoxin is used in the treatment of congestive heart failure, the appearance of signs of cardiac disorder must be watched for carefully, not only clinically but with the electrocardiograph, and such appearance should call for the immediate discontinuance of the drug.

**Summary.** 1. In 13 months digitoxin poisoning was seen in 30 patients who had received the regularly prescribed doses of this isolated digitalis glucoside.

2. The age and sex of the patient or the type of underlying heart disease had no relation to the occurrence of the digitoxin poisoning.

3. Symptoms, such as are known to be due to digitalis overdosage, occurred infrequently in these patients.

4. Signs of disorders of the cardiac mechanism, especially the more serious conduction disturbances, were the earliest and most frequent clinical and electrocardiographic manifestations in these cases of digitoxin poisoning.

5. Considerable caution should be

exercised in the administration of the digitoxin preparations in the regularly advised dosage and form to any patient suffering with congestive heart failure, because the action may be rapidly intoxicating to the cardiac musculature and its conduction system.

6. The factor of safety for this particular *Digitalis purpurea* glucoside seems to be extremely narrow.

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# MULTIPLE MYELOMA

## A REPORT OF EXPERIENCE WITH STILBAMIDINE\* †

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Multiple myeloma is a fairly common, progressive, fatal disease. No therapy used has been curative. Treatment with X-ray has been useful, but it has been only palliative and does not always relieve the pain which is often the most disabling feature of the disease. Snapper<sup>1,2</sup> has recently reported that the injection of stilbamidine exerts a favorable influence on the pain in many cases of multiple myeloma. His report emphasizes that the disease is not cured; however, relief from pain has persisted for many months.

Snapper and his associates<sup>2,3,4,5</sup> also observed that basophilic cytoplasmic precipitates appear in myeloma cells following treatment with stilbamidine. This observation is of great interest, and it may be one of great value in the study of this disease as well as others in which protein metabolism has been disturbed. Histochemical studies demonstrated that these basophilic granules contain a conjugation product of ribose nucleic acid and stilbamidine.

**Material and Methods.** Four cases of multiple myeloma are presented in this report. In each case, the diagnosis was proved by sternal marrow aspiration, tis-

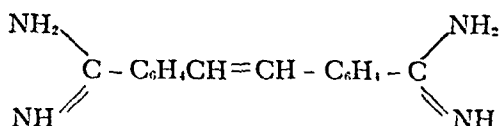
tue biopsy, or postmortem examination. Three of the cases were from the hematology service of the Veterans Administration Hospital, Portland, Oregon, and one case was from the hematology service, University Hospitals and Clinics, University of Oregon Medical School, Portland, Oregon.

All of these cases were treated with stilbamidine. The procedure outlined by Snapper<sup>2</sup> was followed closely. For each injection, the compound was dissolved in 10 ml. of distilled water and given within a short time of its preparation, since the solution must be administered while fresh. An initial intravenous injection of 50 mg. was given, followed 2 days later by an injection of 100 mg. Subsequently, 150 mg. intravenous injections were given every other day. The patients were hospitalized for the course of treatment. Since a diet low in animal protein is an essential part of the treatment, hospital dieticians supervised the diets daily.

Reactions to stilbamidine are mild. Those which occur early are vasomotor phenomena, a fall in blood pressure, sweating, nausea, vomiting, and venous thrombosis at the site of injection. The administration of 1/150 grain of atropine sulphate hypodermically before each injection dissipated many of these reactions. Adrenalin was found to be ineffective

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†The stilbamidine used in this study was supplied by Merck and Company, Inc., Rahway, N. J., through the courtesy of Dr. D. F. Robertson. It is a diamidine compound, 4,4-diamidinostilbene, with the formula



in combatting them. Dissociated trigeminal nerve anesthesia, a later toxic sign, was not noted in this group of cases.

Chronic renal disease is a contraindication to therapy with stilbamidine. One case (number 2) demonstrated a mild degree of renal impairment, but it was not felt to be of sufficient severity to warrant withholding the drug.

Sternal marrow aspirations were performed before the course of treatment with stilbamidine was started and following its completion. The marrow smears were stained with Wright's stain and by the modified Giemsa technique proposed by Snapper and his associates<sup>4</sup> for the demonstration of the basophilic cytoplasmic inclusion bodies in the myeloma cells.

**Case Reports.** The following 4 cases were treated with stilbamidine injections combined with a diet low in animal protein.

**Case 1.** W. W., a 35-year old white male, felt perfectly well until May, 1946, when he developed pain in the lower part of his back while lifting a heavy boat. He was able to do light work until the middle of June, 1946, at which time he began to notice that his legs were weak. He was admitted to the U. S. Naval Hospital, Seattle, Washington, in July, 1946, where radiograms of the spine revealed multiple bony involvement of an osteolytic character and a pathologic fracture of the 8th dorsal vertebra. He received a short course of radiation therapy and was then transferred to the Veterans Hospital, Portland, Oregon, on August 28, 1946. At this time, he complained of increasing weakness, more severe pain radiating from the back anteriorly, and pain on movement of his hips.

Examination on admission revealed a pale individual who appeared to be in a great deal of pain. There was tenderness over the lower dorsal and lumbar spine. There was no evidence of involvement of the spinal cord or of the peripheral nervous system.

His red blood count was 2.9 million and his hemoglobin 55%. The total white blood count was 3,600, with a normal differential cell count. The sedimentation rate was 55 mm. per hour (Wintrobe). The serum calcium was 15 mg. per 100

ml., phosphorus 2.7, acid phosphatase 6.2, and alkaline phosphatase 20.2. The serum total protein level was 6.5 gm. per 100 ml., with 4.8 gm. of albumin, 1.7 gm. of globulin, and an A/G ratio of 2.8 to 1. The urine did not contain Bence-Jones protein. Sternal marrow aspiration revealed 78% plasma cells, 14% staff cells, 7% neutrophils, 3% lymphocytes, and 4% nucleated red cells.

Radiograms of the spine revealed a multiple bone involvement with compression collapse of the 7th and 8th dorsal vertebrae, and all the lumbar vertebrae. There was also widespread involvement of the skull, the scapulae, the humeri, and the femurs.

He received a short course of urethane during October and November, 1946, but it was discontinued because of his persistent vomiting. On May 3, 1947, a course of stilbamidine was started. He was given a total of 30 intravenous injections on alternate days up to a final dosage of 4.5 gm.

His hospital course was progressively downhill. His blood count dropped continuously despite repeated transfusions of whole blood, and his final red blood cell count was 1.2 million and his hemoglobin 27%. His pain became more severe. On July 14, 1947, he lapsed rather abruptly into coma. He showed athetoid movements, but there were no localizing signs. He died 2 days later.

Postmortem examination confirmed the widespread bony involvement demonstrated by X-ray. In many areas there was complete destruction of osseous structures by plasma cell tumors. There was no evidence of regression of the process noted at necropsy. The myeloma cells contained basophilic cytoplasmic granules.

**Case 2.** R. T., a 45-year old colored female, felt perfectly well until September, 1946, when she developed pain in her left arm while picking beans. The pain was progressive, worse at night, and made it difficult for her to grip objects tightly in her left hand. She also complained of numbness of the left arm. She was examined at the University of Oregon Medical School Outpatient Clinic on September 13, 1946, and admitted to Mult-

nomah County Hospital. A neurologic examination revealed no sensory or motor changes. A lumbar puncture several days later revealed normal cerebrospinal fluid and dynamics. Radiograms of the wrist and hand showed no abnormalities. She was discharged from the hospital with the diagnosis of arthritis. While being followed in the Outpatient Clinic, she developed a severe anemia and was readmitted to the Multnomah County Hospital for several days for a transfusion of whole blood. She did not improve with therapy designed to combat her "arthritis" and anemia. She developed increasingly severe pain in the right shoulder, right hip, and right knee, and was readmitted to the Multnomah County Hospital on February 7, 1947.

On admission to the hospital, she appeared to suffer a great deal of pain with movement. Her mucous membranes were pale, and she was unable to move her right hand. Her red blood cell count was 3.0 million and hemoglobin 66%. The total white blood cell count was 6,200, with a normal differential cell count. The sedimentation rate reached 77 mm. per hour. The serum calcium was 15 mg. per 100 ml., serum phosphorus 5, and acid phosphatase 10.2. The serum total protein level was 6.9 gm. per 100 ml., with 4.8 gm. of albumin, 2.1 gm. of globulin, and an A/G ratio of 2.3 to 1. The Congo red test showed disappearance of 39% of the dye in 1 hour. The urine contained Bence-Jones protein. The specific gravity of the urine varied between 1.007 and 1.014; the urine was otherwise normal. The blood urea nitrogen was 28 to 48 mg. per 100 ml. Sternal marrow aspiration revealed only 3% plasma cells. Sternal biopsy confirmed the diagnosis of multiple myeloma. Radiograms of the right shoulder, right arm, skull, and pelvis revealed marked osteolytic involvement with typical punched out areas.

A course of stilbamidine was started on February 26, 1947. She reacted rather severely to the compound, and it was frequently necessary to space her doses farther than 2 days apart. However, she received a total of 13 intravenous injections, totaling 1.8 gm., over a period of

6 weeks, ending on April 11, 1947. After the 3rd injection, she noticed a temporary cessation of her discomfort, but the pain soon returned and became more severe.

While she was receiving the stilbamidine, she developed a lesion on her tongue which was thought to be myelomatous, but a biopsy of the area revealed only focal ulceration. She became aphonic shortly afterward, and direct examination of her vocal cords showed a central type paralysis. Following this episode, her course was progressively downhill, and she expired on April 22, 1947, death apparently due to asphyxia. Autopsy was not permitted.

Case 3. J. M. L., a 28-year old white male, developed disabling pains in the lumbar region in October, 1943, and was admitted to an army hospital. After 3 months, he suddenly developed paralysis of his legs below the hips. A laminectomy was performed, and he recovered movement in the right leg but the left remained completely paralyzed. Examination of a biopsy specimen of the osseous lesion proved it to be a myeloma or plasmacytoma, presumably solitary. Urinary control remained somewhat impaired, but rectal function was good. He was a wheelchair patient in several hospitals until September, 1946, when his wheelchair tipped over. Following this, for the first time he noticed pain at the root of his neck, and numbness of the thumb which gradually spread to involve all the fingers of the left hand. He also complained of numbness of the ulnar aspect of the right hand.

Examination on admission to the Veterans Administration Hospital, Portland, Oregon, on February 27, 1947, revealed a well nourished male who suffered marked pain on any movement. There was weakness and clonus of the right leg and ankle, complete paralysis, clonus, and a positive Babinski on the left leg, and sensation was diminished over both legs. There was diminished sensation over the entire arm and the ulnar portion of the right arm, and there was a positive Hoffman's sign on the left.

His red blood cell count was 4.9 million and hemoglobin 87%. The total white



blood cell count was 8,100, with a normal differential cell count. The sedimentation rate was 37 mm. per hour (Wintrobe). The serum calcium was 9.7 mg. per 100 ml., the phosphorus 3.75 mg., and the alkaline phosphatase 16.6 mg. The serum total protein was 7.2 gm. per 100 ml., with 4.2 gm. of albumin, 3.0 gm. of globulin, and an A/G ratio of 1.4 : 1. The urine contained Bence-Jones protein. Sternal marrow aspiration revealed 4% plasma cells, 2% myeloblasts, 5% promyelocytes, 8% myelocytes, 10% metamyelocytes, 17% staff cells, 25% neutrophils, 14% lymphocytes, and 15% nucleated red cells.

Radiograms of the cervical and dorsal spine revealed extensive bone destruction, and similar areas of destruction were demonstrated in the skull, ribs, and pelvis. The multiple nature of his diseases was apparent in these films.

During April, 1947, he received a course of radiation therapy to the cervical spine. After 1500 r, he experienced slight relief of pain, and he regained considerable strength in the left arm.

On May 3, 1947, a course of stilbamidine was started. He was given a total of 30 intravenous injections, on alternate days, up to a final dosage of 4.5 gm.

He continued to have severe pain in his back, and in addition, he had severe cramping abdominal pains which were apparently due to intramural tumors of the ascending colon and to a massive myelomatous enlargement of the medial surface of the left wing of the ilium. His course was continually downward, and he expired on October 5, 1947. Autopsy was not permitted.

**Case 4.** K. M. E., a 61-year old white male, was in good health until May, 1945, when he was involved in an automobile accident in which several dorsal vertebrae were fractured. In June, 1946, he developed severe pain in the middle of his back which radiated to the anterior chest and lower ribs. This pain has persisted to the present time. A sternal marrow aspiration was done in October, 1946, and a diagnosis of multiple myeloma was made. He has been hospitalized most of the time since November, 1946, first at

Madigan General Hospital, Tacoma, Washington, and later at the Veterans Administration Hospital, Portland, Oregon, where he is still a patient.

Examination on admission to the Veterans Administration Hospital on June 13, 1947, revealed an obese individual, quite comfortable at bedrest but complaining of great pain with movement. There was tenderness over the dorsal vertebrae and several of the ribs, and there was crepitation suggestive of rib fractures. There was diminished sensation over the radial aspect of his left hand and forearm.

His red blood cell count was 3.4 million, with 68% hemoglobin. The total white blood cell count was 6,800, with 51% lymphocytes, 44% granulocytes, and 5% eosinophils. The sedimentation rate was 63 mm. per hour (Wintrobe). The serum calcium was 12.5 mg. per 100 ml., the phosphorus 4.0, acid phosphatase 7.6, and alkaline phosphatase 28.5. The serum total protein level was 8.4 gm. per 100 ml., with 4.35 gm. of albumin, 4.05 gm. of globulin, and an A/G ratio of 1.07 to 1. The urine did not contain Bence-Jones protein. Sternal marrow aspiration revealed 37% plasma cells, 7% myeloblasts, 3% myelocytes, 4% metamyelocytes, 6% staff cells, 8% neutrophils, 24% lymphocytes, and 11% nucleated red cells.

Radiograms of the entire vertebral column, pelvis, and skull revealed a diffuse process of extreme demineralization of all the bony structures. In the pelvis, there were large circular areas of bone destruction, and throughout the entire skeletal system there was riddling of small varying-size circular punched-out areas. This was true also of the skull and all of the ribs. The vertebral bodies showed varying degrees of collapse.

On June 30, 1947, a course of stilbamidine was started, and he received a total of 30 intravenous injections, on alternate days, up to a final dosage of 4.5 gm. Bone marrow smears after treatment was completed revealed the typical basophilic cytoplasmic granules in the myeloma cells.

His pain has become progressively more severe, and he is almost completely bedridden because of it. His anemia has become more marked.

**Discussion.** Bone pain was the out-

standing symptom of which each of the patients complained; 2 had fairly severe pain and 2 had only mild pain. Additional patients without pain were not treated. This series of cases was otherwise unselected. In only 1 instance was pain actually relieved, and this relief was only transitory. The 3 patients who expired were not regarded as being terminal when treatment with stilbamidine was started.

Sternal marrow aspirations were done on each case following the completion of the course of treatment with the drug. Three of the cases received a total of 4.5 gm., and 1 received 1.8 gm. Basophilic cytoplasmic inclusion bodies were found in the myeloma cells of 3 of the cases. Case No. 3 did not have enough myeloma cells in his sternal marrow smear to demonstrate granules, and, as a postmortem examin-

ation was not done, the tissues were not analyzed for the presence of stilbamidine<sup>4</sup>. Since no aspirations were performed until after the treatment had been completed, an estimation of the amount of drug necessary to produce inclusion bodies in the myeloma cells was not made. This was studied by Snapper and his associates.

**Summary and Conclusions.** Four patients with multiple myeloma were treated with stilbamidine. None of them received any degree of persistent symptomatic relief, and there was no evidence that the progress of the disease had been checked in any of the patients. Three of the patients expired within a short time after their course of treatment had been completed. Basophilic cytoplasmic granules were found in the myeloma cells following treatment with stilbamidine.

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# CORRELATION BETWEEN THE CHOLECYSTOGRAM AND THE SECRETIN TEST FOR GALL BLADDER FUNCTION

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Shortly after the discovery of secretin and its effects on the pancreas it was found that extracts of intestinal mucosa also had cholagogue and choleretic effects. The cholagogue action has in recent years been studied in several laboratories and, mainly through the efforts of Ivy and his co-workers (1928, 1937), has been found to be due to an active principle of the small intestine (cholecystokinin) which is distinct from secretin. The choleretic action of intestinal extracts is probably due to at least 2 distinct principles (Friedman and Snape, 1945). One of these has been designated hepatocrinin; it stimulates the liver to secrete bile but is without effect on the pancreas. The other is secretin, which excites both the liver and the pancreas. Evidence that purified preparations of secretin excite the flow of liver bile as well as pancreatic juice has been offered by Mellanby (1927, Still, McBean and Ries (1931-32), Agren (1934), Friedman and Snape (1945), and others. The secretin prepared by the procedure of Friedman and Thomas (1947) has been found to have the dual effect on the liver and pancreas which other investigators have reported for secretin prepared by different procedures (Pinchus, Friedman, Snape, and King, 1945).

The property of secretin to stimu-

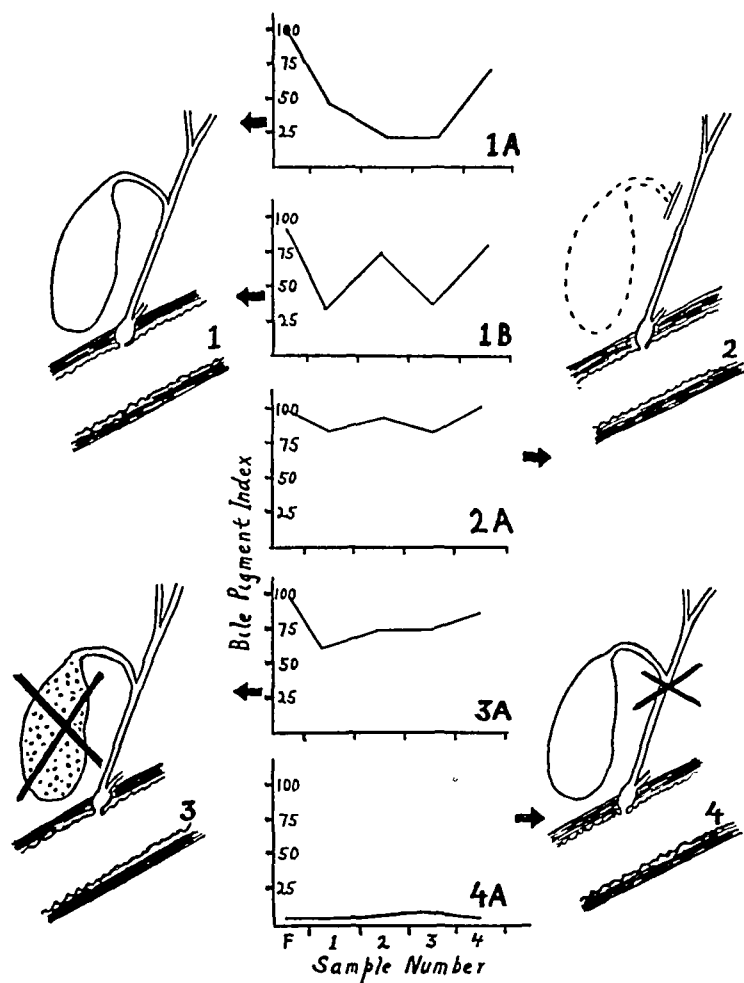
late the flow of liver bile as well as the flow of pancreatic juice has been utilized as a test of gall bladder function (Agren and Lagerlöf, 1937; Diamond, Siegel, and Myerson, 1940). In the normal subject the increased amount of bile secreted by the liver following secretin administration is taken up by the gall bladder where it is subjected to concentration. Following secretin injection the duodenal content thus consists mainly of pancreatic juice and occasionally some bile. The icterus index curve of the duodenal content shows only an occasional high point after the secretin injection and is generally of the configuration shown by Figs. 1A or 1B or some variant of these.

In individuals with cholecystectomy the storage space for the secretin-stimulated liver bile is absent and consequently the bile flows directly into the intestine so that all samples of duodenal content consist of pancreatic juice with a high color index (Fig. 2A). In the patient with a non-functioning gall bladder the condition is essentially similar to that in the cholecystectomy patient, in that the secretin-stimulated liver bile enters directly into the duodenum (Fig. 3A).

In the patient with obstruction of the bile ducts there is complete absence

of bile pigment from the intestinal contents (Fig. 4A). In such cases there is, of course, the obvious jaundice. In non-obstructive jaundice of hepatic origin there is usually a normal type of biliary pigment curve for the intestinal content, except when hepatic damage is severe enough to interfere with the secretory functions of the liver.

In the present study the secretin test was used on 64 patients. Except for 10 patients with cholecystectomy, each patient also had a thorough radiologic examination of the gall bladder. The correlation between the findings of the 2 tests is reported. For the purpose of this study it is necessary to emphasize that the secretin used was free from cholagogic effect as deter-



Figs. 1A, 1B, 2A,—4A. Bile pigment indices of duodenal contents. (See text for details.)

Agren and Lagerlöf (1937), Elvin (1939), and Diamond, Siegel, and Myerson (1940) were among the first investigators to use secretin as a test of gall bladder function. They, as well as Pollard, Miller, and Brewer (1942), and Andrus, Lord, and Lake (1942) found the test to accord well with the clinical findings. In most of the patients studied cholecystographic examination was not performed.

mined by the method of Snape, Friedman, and Thomas (1948).

**Methods.** Subjects selected for study were volunteers, ambulatory patients attending various out-patient clinics of the hospital, and patients from the medical and surgical wards. The subjects presented themselves in the Gastro-intestinal Clinic after an overnight fast. A double-lumen tube of the Lagerlöf type was passed into the intestine and exact posi-

tion of the tube checked by fluoroscopy. The gastric and duodenal contents were collected separately by continuous aspiration at a negative pressure of 30 to 50 mm. Hg. In each case a basal control period of 20 to 30 minutes duration was instituted before injection of the secretin. Secretin, prepared by the procedure of Friedman and Thomas (1948) was then given intravenously at a dosage level of 1.1 clinical units (Agren and Lagerlöf, 1936) per kilogram body weight. (In a few instances the standard dose of 80 clinical units of secretin was given without reference to body weight; this was found to be equally satisfactory). Constant

served as an index of gall bladder evacuation, and added another criterion of gall bladder function.

**Result.** The results of the secretin test and the cholecystogram are summarized in Table 1. Classification of the patients in this table is on the basis of clinical findings and pertinent laboratory data.

Included among the 64 subjects studied were 8 patients with diseases not referable to the digestive system and 7 patients in whom exact diagnosis was not established. In 13 of these

TABLE 1.

## Results of Secretin Test and Cholecystogram in 64 Patients

Clinical Diagnoses	No. Cases	Both Tests Functioning	Both Tests Non-function	Disagreement between tests
Gastro-intestinal disease .....	47			
Cholecystectomy .....	10		10*	
Gall bladder disease .....	9	2	5	2
Liver Disease .....	2	1	1	
Pancreatitis .....	11	6	4	1
Ulcerative colitis .....	7	3	1	3
Diarrhea .....	4	3		1
Miscellaneous .....	6	6		
Non-gastro-intestinal diseases .....	8			
Psychoneuroses .....	3	3		
Miscellaneous .....	5	5		
Not diagnosed .....	7	5		2
Total Number Cases .....	64	34	21	9

\*Only secretin tests were performed on the patients with cholecystectomy.

aspiration of the gastric and duodenal contents was continued for the next 60 minutes, with the samples being divided into fractions collected at the end of 10, 20, 40 and 60 minutes. The bile pigment concentration in the duodenal drainage material was determined by the method of Malloy and Evelyn (1937).

Radiologic visualization of the gall bladder was performed with Priodax (beta-(4-hydroxy-3, 5-diiodophenyl)-alpha-propionic acid). This was given in dose of 3 gm. after a light fat-free evening meal. Approximately 15 hours after the ingestion of the Priodax, and while still fasting, the patient was subjected to roentgenography in the usual manner. After partaking of a fatty meal the patient was restudied roentgenographically 1 hour later to determine the amount of shrinkage of the gall bladder shadow. This

15 cases both the secretin test and the cholecystogram showed a functioning gall bladder. In the remaining 2 cases (Table 2: Miss A. M.; Miss H. M.) the cholecystogram was essentially normal but the secretin test (performed twice on each patient) showed the gall bladder incapable of taking up all of the liver bile.

In 10 of the patients, the gall bladder had been removed surgically at some time (3 months to 12 years) prior to our study. Cholecystograms were not taken in these patients. As might be expected, the secretin tests yielded intestinal contents of high icterus index (Fig. 2). Four of these patients were regarded as showing post-cholecystectomy symptoms, but at the time of

study neither sphincteric spasm nor bile duct obstruction was suggested by the bile pigment curve of the intestinal contents.

The diagnosis of gall bladder disease was established in 9 patients. In 5 of these patients the secretin test and

the roentgenographic findings agreed with the clinical diagnosis of non-functioning gall bladder. In 2 patients both the cholecystogram and the secretin test indicated good gall bladder function. In one patient the secretin test showed a non-functioning viscus,

TABLE 2.

Summary of Data in 9 Cases with Disagreement between Secretin Test Result and Cholecystogram.

**Miss A. M.:** age 32, 115 lb. Right uretral stricture and ptosis of right kidney. Normal cephalin-cholesterol flocculation. Other laboratory data negative. Cholecystogram April 2, 1947: gall bladder well visualized, and evacuates well. Secretin test Sept. 20, 1946, and March 28, 1947: gall bladder non-functioning on both occasions.

**Miss H. M.:** age 35; 88 lb. Low grade fever of unknown origin. Possible uretro-pelvic stricture. Liver function test (bromsulphalein, cephalin-cholesterol flocculation, thymol turbidity, van den Bergh) all negative. Cholecystogram Nov. 15, 1946: gall bladder well visualized. Secretin test Sept. 30, 1946, and Oct. 4, 1946: gall bladder non-functioning on both occasions.

**Mrs. A. A.:** age 24; 134 lb. Cholecystitis and cholelithiasis. Right upper quadrant pain of colicky nature. Marked psychic overlay. Cholecystogram Oct. 17, 1946: gall bladder poorly visualized, floating calculi. Secretin test Oct. 11, 1946: gall bladder non-functioning.

**Mrs. O. H.:** age 31; 105 lb. Cholecystitis and diabetes, chronic alcoholism. Acute pancreatitis, onset of symptoms Oct. 18, 1946. Cholecystogram Oct. 25, 1946: gall bladder non-functioning; repeated cholecystogram Oct. 30, 1946: gall bladder visualized, (calculi?). Secretin test Oct. 31, 1946: gall bladder non-functioning.

**Mr. G. P.:** age 27; 135 lb. Pancreatic fibrosis and diabetes. Nocturnal diarrhea. Laboratory: histamine-resistant achlorhydria; spinal fluid protein 216, 264, 608 mg. per 100 cc. on 3 occasions; fasting blood sugar 380 mg. per 100cc.; high fat content in stool; Wassermann negative. Cholecystogram Sept. 26, 1946: gall bladder not visualized. Secretin test Sept. 23, 1946 and April 30, 1947: functioning gall bladder on both occasions. Died October, 1947. Post-mortem findings: small firm pancreas with congestion and fibrosis, no cysts. Gall bladder normal, no stones, ducts patent.

**Mr. D. McG.:** age 31; 124 lb. Non-specific ulcerative colitis without marked bowel frequency. Liver function tests negative, pancreatic function normal. Other laboratory data negative. Cholecystogram June 17, 1947: gall bladder well visualized with good evacuation. Secretin test June 6, 1947: gall bladder non-functioning.

**Mr. J. A.:** age 18; 136 lb. Non-specific ulcerative colitis without diarrhea. Liver and pancreatic functions normal. Urine negative. Cholecystogram June 24, 1947: gall bladder well visualized and evacuates well. Secretin test June 6, 1947: gall bladder non-functioning.

**Mrs. M. C.:** age 42; 130 lb. Non-specific ulcerative colitis with marked tendency to constipation. Liver and pancreatic function tests negative. Cholecystogram Sept. 29, 1947: gall bladder well visualized and evacuation good. Secretin test June 23, 1947: gall bladder non-functioning.

**Mrs. C. D.:** age 53, 89 lb. Non-tropical sprue, osteoporosis; diarrhea with large quantites stool fat. Serum phosphorus 1.85, serum calcium 6.8 mg. per 100 cc. Small bowel deficiency pattern by X-ray. Cholecystogram Jan. 22, 1947; faint shadow suggesting impaired gall bladder concentrating power. Secretin test Jan 3, 1947: gall bladder functioning. Died Aug. 15, 1947. Post-mortem findings: acute necrosis of liver, atrophy of mucosa of stomach and ileum, pancreas normal, gall bladder large, thin, distended with bile, no bile duct obstructions.

which, although visualized roentgenologically, showed small calculi floating in the upper third (Table 2: Mrs. A. A.). In the 9th patient (Table 2: Mrs. O. H.) a cholecystogram showed the gall bladder to be non-functioning; when repeated 5 days later the gall bladder could be visualized. The secretin test led to the conclusion that the gall bladder was not functioning.

Two patients with jaundice at the time of the studies are included in the series. One patient gave a normal type of biliary pigment curve for intestinal contents by the secretin test and showed a gall bladder which could be well visualized. The patient was believed to have a mild hepatitis which abated spontaneously with disappearance of the jaundice in about ten days. The other patient was suspected of having obstructive jaundice. Both tests showed the gall bladder to be non-functioning. At operation a carcinoma of the head of the pancreas with involvement of the common duct and gall bladder was found.

Eleven of the patients at the time of our study were diagnosed as having chronic pancreatic insufficiency. In 7 cases the diagnosis was confirmed by biopsy or at operation or necropsy; in the other 4 cases the diagnosis was made on laboratory findings (including the secretin test for pancreatic function). In 5 of these patients the cholecystogram and secretin tests showed the gall bladder capable of concentration, while in 4 patients both tests agreed in showing a non-functioning gall bladder. In 1 case with diarrhea the gall bladder could not be visualized radiographically, but showed a normal type of bile pigment curve with the secretin test. The pertinent data in this patient are shown in Table 2 (Mr. G. P.).

Of 16 patients diagnosed as having gastro-intestinal disorders which did not involve primarily the biliary tract,

liver or pancreas, there was disagreement between the results of the 2 tests in 3 cases (Table 2: Mr. D. M. G.; Miss J. A.; and Mrs. M. C.). These 3 patients were all among a group of 7 who had non-specific ulcerative colitis; in each the gall bladder was well visualized but the secretin test suggested a non-functioning viscus. A 4th patient showed an abnormal gall bladder by both tests, while in the remaining 3 ulcerative colitis patients the gall bladder was considered normal by both tests.

Normal gall bladder functions were shown by both tests in 2 patients with diarrhea who gave no evidence of organic lesions of the colon or of pancreatic insufficiency. In a 3rd patient, diagnosed as having non-tropical sprue, the cholecystogram showed a faint gall bladder shadow suggesting impaired function, but the secretin test suggested a functioning organ (Table 2: Mrs. C. D.).

**Discussion.** The cholecystographic test and the secretin test are both measures of the gall bladder's capacity to fill and concentrate hepatic bile. Interpretation of the results of each test must take into consideration the influence of certain factors, only some of which are common to both tests and some of which are not primarily dependent on the gall bladder.

In the secretin test the period of observation is usually 1 hour, while in the cholecystogram the time between ingestion of the Priodax and the roentgenologic study is between 15 and 18 hours. It is possible that in some cases a gall bladder with only a slight impairment in concentrating functions may during the 15 to 18 hours concentrate sufficient radio-opaque dye to make it visible roentgenographically, and yet not remove during the 1 hour secretin test enough liver bile to alter appreciably the duodenal bile pigment

index from that found in the cholecystectomy patient. Perhaps it may be significant that in 7 of the 9 studies in our present series which showed disagreement between the 2 tests, it was the secretin test that indicated the gall bladder to be "non-functioning."

In the patients with jaundice the recovery of colorless duodenal contents following secretin administration has been interpreted as indicating obstruction of the biliary tract and that the secretory functions of the liver are not impaired. However, it must be borne in mind that in extensive liver damage the secretion of bile may be so reduced as to give also a colorless duodenal content. As has already been pointed out, (Golden, 1941), the excretion of radio-opaque dye by the damaged liver may be sufficiently reduced likewise to make interpretation of the cholecystogram difficult.

Particularly important in the oral cholecystogram is the absorptive state of the intestine. When malabsorption is suspected, as in diarrhea of pancreatic origin, in coeliac disease, and in so-called idiopathic hypermotility of the bowel, the intravenous type of cholecystogram is suggested. Presumably, in such cases, the secretin test would be more informative than the oral cholecystogram. This is shown in cases G. P. and C. D. (Table 2): the secretin test in each was normal but the cholecystogram was not. At autopsy no evidence of gall bladder disease was found in either patient.

Because of close anatomic and physiological relationships the biliary tract and pancreas frequently are found non-functioning in the same individual. In the present series, 4 out of 11 cases with chronic pancreatitis were found to have non-functioning

gall bladders while in another study of chronic pancreatic insufficiency Snape and Friedman (unpublished) concluded that the gall bladder was non-functioning in 8 out of 17 cases. The use of secretin has the advantage in that the functional states of both pancreas and gall bladder may be determined simultaneously. However, secretin as a test of gall bladder function has its limitations in that it indicates only the capacity of the gall bladder to concentrate bile: the presence of bile stones is shown only by radiologic studies. Microscopic examination of the duodenal contents following secretin administration may be helpful.

**Conclusion and Summary.** Cholecystographic and secretin tests of gall bladder function were performed in a series of 64 patients. In 55 patients the conclusions drawn from both tests were the same, while in 7 cases the findings from the secretin test disagreed with those from the cholecystogram. In 2 of these 7 cases the secretin test and subsequent autopsy both revealed the gall bladder to be normal, but the cholecystogram suggested a non-functioning organ. In 2 other cases the secretin test showed the gall bladder to be non-functioning: the gall bladder, while visualized, was seen to contain calculi.

The secretin test showed a high degree of correlation with the clinical diagnoses. The secretin test is not suggested as a substitute for the much simpler procedure of cholecystographic examination. However, we think it is a useful supplement to the usual procedures and recommend it when the data from the cholecystogram are difficult to interpret.

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# PSEUDOMONAS SEPTICEMIA AND ENDOCARDITIS

## Report of a Case

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*PSEUDOMONAS AERUGINOSA* (*B. pyocyaneus*) is frequently found on normal skin and is commonly associated with infection of the skin and the urinary tract. Rarely, this organism acquires more invasive properties, and produces widespread lesions<sup>2,4,5</sup>. In the case here reported an infection by *pseudomonas aeruginosa* led to generalized sepsis with protracted involvement of many organs, and to massive endocarditis. The rarity of this condition prompts the present case report.

**Case report:** G.S., a 40 year old white man, was admitted to the Service of Dr. I. S. Ravdin on 10-28-46 with complaint of severe abdominal pain. Eighteen days prior to admission he was dazed for 2-3 hours following an automobile accident. For several years he has experienced episodes of hematemesis and 3 days after the accident he had vomited a quantity of bright red blood. The following day he experienced sharp severe epigastric pain which persisted until admission. No jaundice or elevation of temperature had been present.

**Physical examination** revealed a blood pressure of 110/70, a rectal temperature of 101°F, a pulse of 80, and respirations of 28 per minute. The patient was well developed and well nourished. He appeared to be acutely ill. The respirations were shallow; the heart sounds were good and there were no murmurs heard. The heart was not enlarged to percussion. The abdomen was distended; peristalsis was normal. There was generalized abdominal tenderness, most marked in the epigastrium.

**Laboratory data:** Hemoglobin 11.6 grams %; WBC 100,800 per cu. mm. Serum amylase on admission was 400 Somogyi units per cc. Three days later it reached 1218 units per cc. Urinalyses were repeatedly within normal limits.

The symptoms persisted and the temperature ranged between 101 and 102.4 F. for the next 3 days. The clinical impression was acute pancreatitis.

**Operation:** On 11-2-46, four days after admission, an exploratory laparotomy was performed. The pylorus and first portion of the duodenum appeared normal. The pancreas was not swollen to palpation and there was no evidence of fat necrosis. At the root of the small bowel mesentery extending to the sacral promontory, a large mass of edematous tissue was present. Needle aspiration of this mass yielded cloudy fluid which was rich in amylase. A biopsy of the posterior peritoneal tissue showed the usual findings of inflammation. Culture from the biopsy site grew only a few diphtheroids. The retroperitoneal area was drained transabdominally and the abdomen closed.

Treatment postoperatively included repeated transfusions of whole blood, intramuscular penicillin 37,500 units every 3 hours and streptomycin 0.25 gm. every 4 hours. Penicillin and streptomycin were stopped 4 days postoperatively because of the appearance of a skin rash which subsided rapidly after the drugs were withdrawn.

The postoperative course was marked by a septic temperature which lasted until 11-13-46. There was a rather copious watery drainage through the abdominal

drainage tract which contained over 3200 units of amylase per cc. The drainage decreased gradually and the patient regained strength. He was discharged on 11-27-46 with only slight drainage persisting.

His course was uneventful until 12-29-46 when he suddenly experienced severe epigastric pain which radiated through to the back. This pain remained constant for 4 days. Following this he was asymptomatic until 1-16-47 when a similar episode recurred and again subsided in a day or two. On 2-12-47 he was suddenly stricken with severe back pain which radiated to the left loin. This continued until admission on 2-14-47.

Physical examination at this time revealed a blood pressure of 92/55, pulse of 72, and temperature of 98.6. The patient complained of considerable pain made worse by recumbency. Extreme abdominal tenderness and rigidity were present, especially in the mid-epigastrium. The lungs were normal. There was no cardiac enlargement and no murmurs were present. Heart rhythm was normal and the pulse was full and slow.

**Laboratory data:** Hemoglobin 13.6 grams %, WBC 18,900 per cu. mm. with 79% neutrophils. Serum amylase 275 units per cc. Urinalysis was within normal limits.

**Operation:** Laparotomy revealed a very much enlarged pancreas which along with the duodenum, and cystic and common ducts was involved in an inflammatory mass. A great deal of edema was present in the retroperitoneal tissues, gallbladder, and posterior gastric wall. No fat necrosis was noted. The peritoneum was split and the head and tail of the pancreas drained with Penrose drains. No stones were palpated in the gallbladder.

Treatment included intramuscular streptomycin 0.25 gm. and penicillin 100,000 units every 3 hours.

The postoperative course was uneventful, and he became afebrile 4 days after operation. Serum amylase ranged from over 400 units per cc. on 2-15-47 to 102 units on 2-28-47. A cholangiogram done on 2-21-47 showed a large common duct with no evidence of obstruction. On 2-26-47 pancreatic studies showed a dis-

sociation of enzymes: low amylase secretion with tryptase and lipase in the normal range. No response to urecholine occurred. This was interpreted<sup>3</sup> as being typical of chronic pancreatitis. The patient was discharged on 3-1-47 much improved.

For about 2 months he was asymptomatic, but on 4-26-47 he was again stricken with severe abdominal pain and repeated vomiting. He was again admitted to the hospital.

**Physical examination:** Temperature 98.2 F., Blood pressure 122/84. There was a suggestion of scleral icterus. The heart was normal in size, and no thrills or murmurs were present. There was moderate tenderness and rigidity of the right upper abdominal quadrant. Peristalsis was decreased. No organs or masses were palpated.

Laboratory data were similar to those of the previous admission. In addition the Van den Bergh reaction was: Direct-immediate, Indirect 7.5 mg%. Serum amylase was over 500 units per cc.

The following day the jaundice rapidly deepened, the temperature rose to 104 F., and the blood pressure fell to 70/40. He vomited 300 cc. of dark brown material, and became somewhat dyspneic. A diagnosis of recurrent pancreatitis, with secondary cholangitis, was made.

**Operation:** After the hypotension was overcome by the use of transfusions of blood and plasma the abdomen was again explored. The gallbladder appeared acutely inflamed and the fundus appeared to be almost gangrenous. The mucous membrane bled freely after the vessels were decompressed. The duodenum was markedly edematous and the pancreas was firm but not enlarged. No other pathologic process was detected. Cholecystostomy was done. Peritoneal culture showed non-hemolytic streptococci and *Pseudomonas aeruginosa*. The latter organism was also grown from the gallbladder bile.

His postoperative condition was at first precarious, but after 10 days his febrile reaction gradually subsided and his jaundice decreased. Serum amylase decreased from 555 Somogyi units per cc. on his first postoperative day to normal levels

a few days later. He was discharged afebrile and without jaundice on 5-25-47 with the cholecystostomy tube in place.

He again did well until 6-3-47 when his temperature suddenly rose to 105.8 F. following a shaking chill. He had 3 subsequent chills in the next 6 days, and he was readmitted on 6-9-47. His only complaints were chills, fever and weakness.

**Physical examination:** Blood pressure 105/50; temperature 103.4 F.; pulse 118; respirations 34 per minute. He was slightly dyspneic. The lungs were clear and the heart appeared to be normal. There was slight epigastric tenderness and the cholecystostomy tube was draining small amounts of bile. Peristalsis was normal.

**Laboratory data:** Hemoglobin 8.9 gms. %; WBC 16,900 per cu. mm.; neutrophils 81%; Van den Bergh: Direct immediate, Indirect 1.1 mg. %.

**Operation:** The fever persisted, but his condition was certainly less acute than on any previous admission, and it was decided that a definitive operation should be done at this time of relative quiescence. On 6-13-47 the abdomen was again explored. The liver was large and soft and a liver abscess was suspected, but several needle aspirations in the liver substance yielded no pus. The pancreas was firmer than normal but not as swollen as at the last exploration. A cholecystectomy was done, and biopsy from the head of the pancreas was taken which proved to be normal pancreatic tissue. The common duct was normal in size, and no stones were palpated.

Blood culture on the first postoperative day, 6-14-47, showed *Pseudomonas aeruginosa* in pure culture. Sensitivity tests of the pseudomonas organisms grown from the blood were as follows: Penicillin—not sensitive to 10 units per cc., streptomycin—sensitive to 500 to 1000 units per cc.

His temperature ranged between 102 and 104.8 F. for the remainder of his course. On 6-15-47 a few petechiae were found in the palpebral conjunctivae, and slight ankle edema was noted. Intramuscular penicillin 100,000 units every three hours was started on admission.

The following day intramuscular streptomycin 0.25 gm. every three hours was also given. More conjunctival petechiae appeared on 6-16-47, and a sternal marrow culture grew *Pseudomonas aeruginosa*. On 6-17-47 blowing systolic aortic and apical murmurs appeared, and slight cardiac enlargement was detected. It was obvious that his condition was not improving, and on the basis of the sensitivity studies on the offending organism, streptomycin was stopped. Through the courtesy of Dr. Frank Meleny a pyocyanus phage (not autogenous) was administered beginning on 6-22-47. (One half cc. diluted 1:10 was given intravenously every 4 hours). Obvious signs of aortic regurgitation developed, and the course was steadily downhill. On 6-23-47 petechiae appeared over the entire body. Despite all efforts at supportive treatment including digitalis he expired on 6-24-47.

**Autopsy (1 hour postmortem):** The body was that of a well developed, well nourished white male weighing 71 kg., and measuring 178 cm. There was generalized edema of trunk, genitalia, and extremities. Numerous conjunctival petechiae were noted. An upper midline abdominal surgical wound was present; this showed superficial dehiscence, but in its deeper portion it was firmly adherent to the liver. About 500 cc. of blood, both fluid and clotted, was present in the peritoneal cavity.

The heart weighed 440 grams. Its surface was studded with petechiae. There was a moderate degree of left ventricular enlargement, the wall measuring 15 mm. in thickness. Engrafted upon the aortic valve were large, soft, pale, fleshy vegetations, up to 8 mm. in height, which almost covered the cusps (Fig. 1). The left leaflet showed a perforation 3 mm. in diameter. No evidence of previous aortic valvular disease was noted. The other valves appeared normal. Microscopically, the endocardium was infiltrated with various types of inflammatory cells; plasma cells predominated, but neutrophils and eosinophils were also present in small numbers. In the myocardium were scattered areas in which the muscle fibers were pale, granular, and vacuolated. In some of these areas there was a slight



Fig. 1.—Heart: The aortic cusps are covered by pale, fleshy vegetations. There is hypertrophy of the left ventricle.

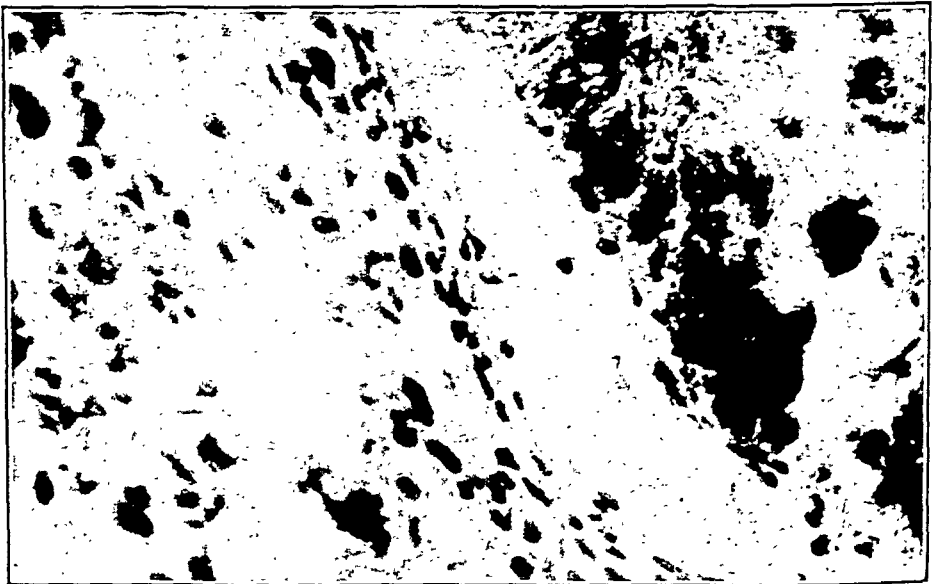


Fig. 2.—Aortic cusp: In the center of the field, and toward the right, is a massive colony of *Pseudomonas aeruginosa* consisting of rod-shaped bacilli extending radially. On the left is tissue reaction consisting of fibroblasts, lymphocytes and plasma cells. (Gram stain 720 $\times$ ).

infiltration of neutrophils, but in most there was little response of inflammatory cells. Plasma cells however were diffusely scattered through the myocardium. In the epicardium, cuffs of plasma cells

extended about some of the small vessels. Section of the aortic vegetation showed a fibrin thrombus which contained large masses of gram negative bacilli (Fig. 2).

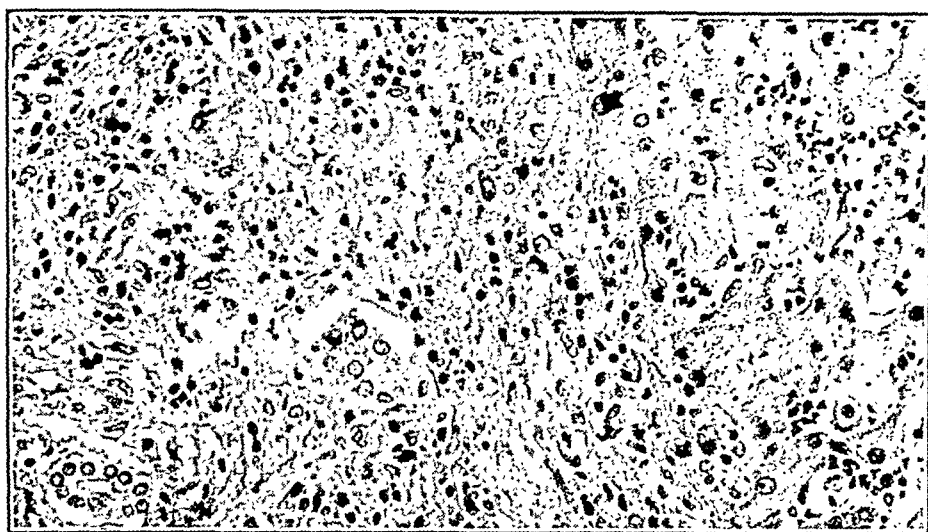


Fig. 3.—Liver: There is extensive increase in periportal fibrous tissue with marked proliferation of small bile ducts. This tissue is infiltrated with plasma cells and lymphocytes. The hepatic cords are atrophic, and the sinusoids contain numerous inflammatory cells. (H and E, 244 $\times$ ).

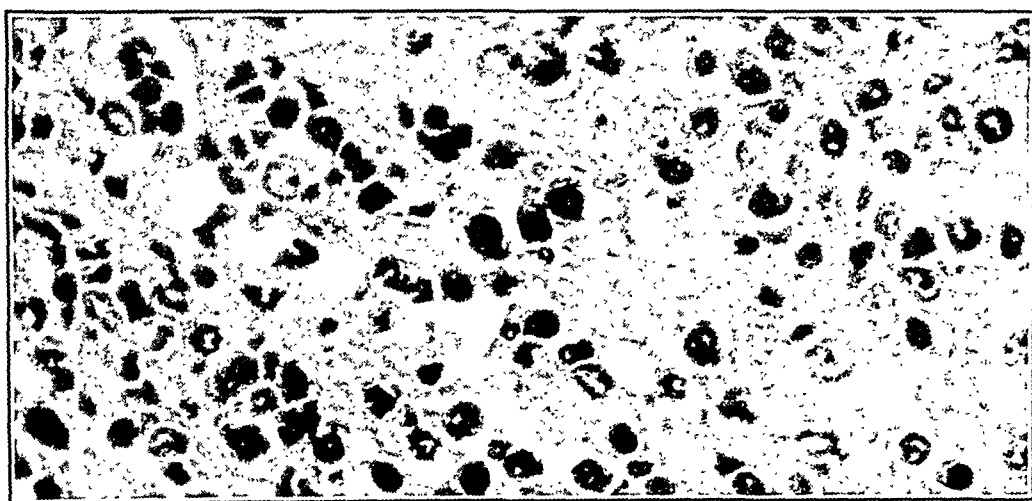


Fig. 4.—Liver: The hepatic cords are shrunken and atrophic. Filling the sinusoids are large numbers of inflammatory cells, principally plasma cells. (H and E, 450 $\times$ ).

The lungs were in a state of passive congestion; no other alterations were detected.

The liver weighed 4650 grams. In the dome were 3 separate abscesses, each approximately 25 mm. in diameter; they were thick-walled and contained yellow pus. Microscopically, the content of the abscesses was composed of necrotic debris, yellow-green crystals, bacilli, neutrophilic granulocytes, and foamy macrophages. The walls were fibrous with numerous macrophages and a few giant cells. The liver in general presented a considerable increase in periportal connective tissue, irregularly distributed, which was associated with a proliferation

of the small bile ducts and an infiltration of plasma cells and lymphocytes (Fig. 3). The hepatic cords were shrunken and atrophic throughout, and the sinusoids were distended with inflammatory cells, principally plasma cells and neutrophils (Fig. 4).

The spleen was considerably swollen, and weighed 640 grams; there were a few small infarcts. Microscopic examination revealed numerous plasma cells in the sinusoids as the most conspicuous alteration.

The pancreas was stony hard, especially so in the region of the head. In this area white nodules of fat necrosis were noted. Microscopically the parenchyma ap-

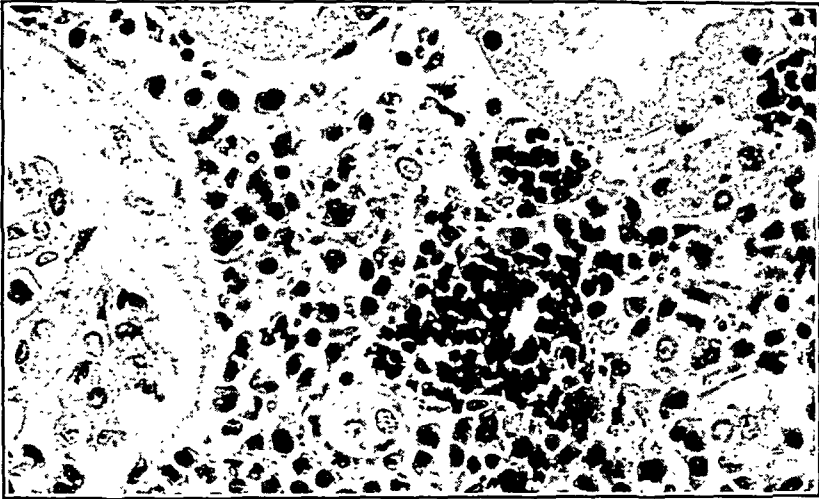


Fig. 5.—Kidney: The tubules are spread apart by dense infiltration of inflammatory cells, principally plasma cells, in the interstitial tissues. (H and E, 450 $\times$ ).

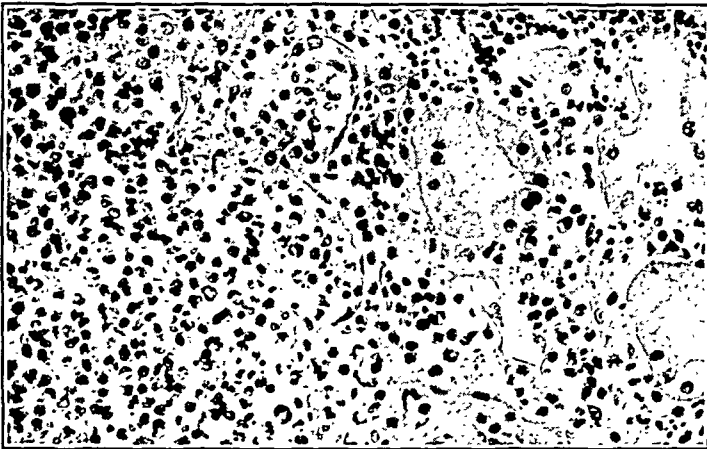


Fig. 6.—Kidney: Edge of a microscopic abscess. The inflammatory cells which are principally polymorphonuclear leukocytes extend between the tubules. (H and E, 262 $\times$ ).

peared normal, but the interlobular tissue was densely fibrosed and contained wall-off foci of necrosis.

The adrenals weighed 14 grams (left), and 21 grams (right). A cortical adenoma measuring 15 mm. in diameter was present in the right gland. Microscopic examination revealed slight interstitial infiltration of lymphocytes and plasma cells.

The kidneys weighed 350 grams (left), and 350 grams (right). They were large, soft, and pale, and the cortex was thickened. Microscopically, linear interstitial infiltrations of plasma cells were seen in both cortex and medulla, principally the latter. (Fig. 5). In addition

there were a few recent minute abscesses in which neutrophils constituted the predominant cell type (Fig. 6). The cells of the convoluted tubules showed extensive hydropic degeneration.

In sections of lymph node and bone marrow extensive infiltration with plasma cells was noteworthy.

Postmortem cultures obtained from 2 liver abscesses, peritoneal fluid, and aortic vegetation all showed *Pseudomonas aeruginosa*.

**Cultural Characteristics of Organism.** On smear the causative organism proved to be a medium-sized Gram-

negative rod, which showed active motility in wet preparations. On agar, rough, spreading colonies were formed, which had a grape-like odor, and which were surrounded by large zones containing yellow-green pigment which was fluorescent under ultra-violet light. In broth a slight pellicle was formed, and the medium was colored green. The pigment was chloroform soluble. None of the laboratory sugars was fermented; gelatin was liquified slowly, and there was questionable production of hydrogen sulfide. Growth occurred in Koser's medium; there was questionable acidification of litmus milk; nitrates were not reduced; indole was not formed, and urea was not split.

This strain was compared by guinea pig inoculation with one of *P. aeruginosa* which was isolated as a non-pathogenic contaminant from a different patient. The pathogenic strain was found to be no more virulent for the guinea pig than was the non-pathogenic strain.

**Comment.** As mentioned in the introduction *Pseudomonas aeruginosa* is a not uncommon pathogen in skin and urinary tract infections, but other severe infections due to this organism are rare. It is probably because of this fact that little importance was attached to the presence of *Pseudomonas aeruginosa* in pure culture in the peritoneal cavity and gallbladder bile of our patient almost 2 months before death. Only when blood culture revealed a septicemia due to this organism, 2 weeks before death, was the causal relationship of the bacillus appreciated. Streptomycin was administered prophylactically in reasonable dosage during each of the postoperative periods, but the organism was found to be practically insensitive.

This suggests two possibilities: either the organism was insensitive to streptomycin from the onset, in which case valuable time was lost by using an

ineffective drug, or the organism developed tolerance. If the latter was true, early treatment with massive doses of the drug might have been effective. In either case, the failure to appreciate the causal relationship of *Pseudomonas* to the disease resulted in therapeutic failure. The acquisition of resistance cannot be over emphasized in considering selection of the most effective drug or agent in ample dosage. It is possible that bacteriophage might have been effective had it been tried before the onset of septicemia and endocarditis. Finally, one or more of the operations might have been avoided had the presence and nature of the infection been recognized earlier.

We believe that, after exclusion of skin contamination, a culture which is positive for *Pseudomonas* obtained from any patient with a febrile illness should prompt the following studies: (1) A blood culture, (2) Serum agglutinins for *Pseudomonas* (a titer of 1:30 or higher is significant)<sup>5</sup>, (3) The sensitivity of the organism to the available therapeutic agents.

Initial dosage should be sufficiently high to prevent the development of resistance of the organism to the agent employed. In the event that the organism is not sufficiently sensitive to streptomycin or penicillin it may be desirable to prepare and administer a specific bacteriophage. Stock *Pseudomonas* bacteriophage might be found to be of value while awaiting preparation of the autogenous phage.

Nine other instances of endocarditis due to *Pseudomonas aeruginosa* have been reported<sup>3</sup>. In only one of these was the aortic valve involved. In our case, the second showing aortic valve involvement; the organism attacked a valve which appeared to be otherwise normal.

The victims of severe or generalized *Pseudomonas* infections are usually debilitated, chronically ill and mal-



nourished. In contrast, this patient was in good health until the onset of his infection. It is likely that the gastro-intestinal tract was the portal of entry and that spread to the liver and pancreas ensued. The liver abscesses probably represented the foci from which the septicemia and endocarditis were derived. The relationship, if any, between this patient's disease and his accident and hematemesis is not clear.

Of particular interest is the pronounced plasma cell reaction in all lesions, indicating a process of relatively long duration as indeed is suggested by the history. Neutrophils predominated in only a few of the lesions. Although plasma cells characterize chronic infections, the number of these cells, and the prominence of young forms is unusual.

**Summary.** A case is reported of protracted sepsis by *Pseudomonas aerugi-*

*nosa* (*B. pyocyaneus*) with lesions in many organs, and massive acute endocarditis involving the aortic valve.

Only one other reported case of endocarditis of the aortic valve caused by *P. aeruginosa* has been found in the literature.

The portal of entry in this case appears to have been the gastro-intestinal tract. From this locus spread occurred to the gallbladder and liver. Abscesses in the latter probably acted as foci for general dissemination of the organism.

The importance of a blood culture positive for *P. aeruginosa* is emphasized, and suggestions are made for further diagnosis studies.

It is essential that prompt treatment be instituted with a drug of proved effectiveness in adequate dosage in order to prevent the development of drug resistance on the part of the micro-organism.

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# FURTHER CLINICAL OBSERVATIONS ON THE USE OF DIBUTOLINE, A NEW ANTISPASMODIC DRUG

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Since our preliminary report<sup>1</sup> on the clinical use of dibutoline (dibutyl urethane of dimethyl ethyl- $\beta$ -hydroxy ethyl ammonium sulfate, Merck), we have had the opportunity of employing this drug in the treatment of many more types of cases exhibiting smooth muscle spasm. Its efficacy as a therapeutic agent in problems of spasticity of the gastrointestinal tract, the biliary tree, the urinary system and the uterus has been clinically observed and will be reported herein.

Swan and White<sup>3</sup> described the synthesis of dibutoline and its use as a cycloplegic and mydriatic. We had previously found this drug useful as an antispasmodic agent, either as the sole therapeutic measure or as an adjuvant, in the treatment of 3 cases of chronic, nonspecific ulcerative colitis, 2 cases of premenstrual cramps, colonic spasm in 4 patients and 1 case each of duodenitis with associated spasm, functional pylorospasm and pylorospasm associated with duodenal ulcer.<sup>1</sup>

**Pharmacological Action.** Dibutoline has been shown to possess a direct inhibitory action on the smooth muscle of the intestine as well as an anti-acetylcholine or atropine-like action.<sup>2</sup> Peterson and Peterson<sup>2</sup> have demon-

strated that in the normal human stomach, dibutoline inhibits the motor activity; higher doses of the drug also decrease tonus.

In clinical usage the drug generally has a qualitative action similar to that of atropine, although certain differences have been observed and will be commented upon. However, distinct quantitative differences between the two drugs have been apparent. First, the pharmacological effects of dibutoline have been observed to occur more quickly than with atropine; in from 1 to 3 minutes after subcutaneous administration effects of dibutoline are noted. Second, a more intense action is effected with dibutoline, but which has a shorter duration than the milder action of a comparable dose of atropine. An analogy may be made in comparing the quantitative actions of dibutoline and atropine to the pharmacological effects of amyl nitrite and sodium nitrite; the former acts almost immediately and with great intensity as compared with the less intense and more persistent effects of sodium nitrite.

**Inhibition of Gastric Secretion.** *Dogs.* In 10 tests on 5 dogs with pouches of the entire stomach dibutoline in a dose of 10 mg. administered subcutaneously

produced an average inhibition of 44% in the output of hydrochloric acid in response to 0.5 mg. of histamine dihydrochloride in a two-dose histamine test. The dogs averaged 10 kg. in body weight so that this represented a dose of about 1 mg./kg. of dibutoline. For comparison 1 mg. of atropine sulfate tested in a similar manner in the same dogs produced 56% inhibition. Therefore we may conclude that dibutoline in a therapeutic dose produces

After 6 ten-minute samples had been collected to establish the basal level of gastric secretion for each patient, dibutoline was given and the gastric drainage was continued for 1 to 2 hours. In these same patients a similar test was performed either 1 week earlier or 1 week later, using 1 mg. atropine sulfate instead of dibutoline. In general the response to dibutoline was similar to that of atropine but of distinctly shorter duration. With atropine the maximal

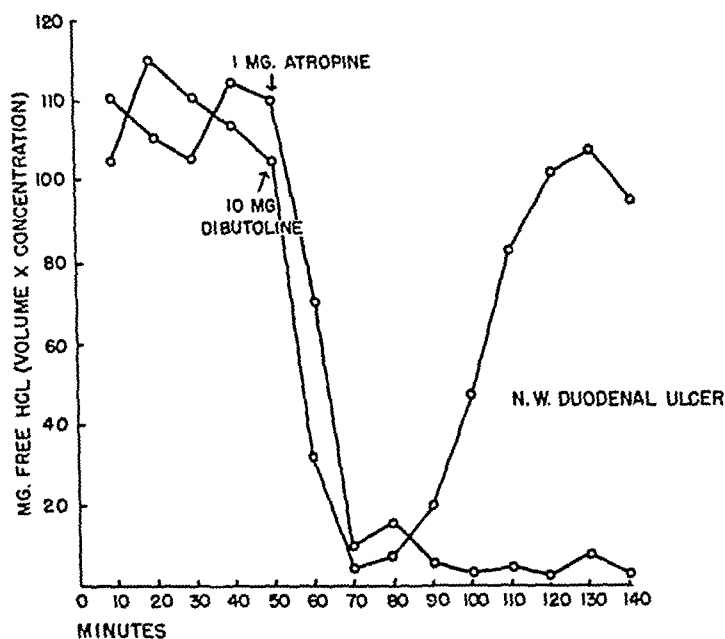


Fig. 1.—Comparison of the inhibitory effect of dibutoline and atropine sulfate on the basal gastric secretion in a duodenal ulcer patient.

almost as great a depression of gastric secretory response to histamine as does atropine in its therapeutic dose range. For both atropine and dibutoline substantial increase in the dose (for example, 50 mg. dibutoline or 3 mg. of atropine) results in only a slightly greater degree of inhibition than the smaller doses. Thus the inhibition produced by these drugs is always partial.

*Man.* Dibutoline (10 mg. subcutaneously) has been administered to 5 patients with peptic ulcer while the gastric secretions were being continuously drawn off by means of a Rehfuß tube.

depression was still present when the test was terminated 1½ hours after administering the drug, whereas with dibutoline the secretory rate had returned to the control level within one hour. In 3 cases both dibutoline and atropine produced complete suppression of free acid secretion and in the other two patients both drugs produced marked but incomplete inhibition of acid secretion. A typical example of the latter type of response is shown in the accompanying graph (Fig. 1).

*Vascular Effects.* In no patient have we observed a distressing tachycardia

following the subcutaneous injection of 10 or 20 mg. of dibutoline. A moderate tachycardia of short duration may occur following the use of doses larger than 10 mg. Capillary nail bed measurements in 3 normal human subjects have revealed no significant calibre change of the loops after subcutaneous administration of 10 or 20 mg. of the drug. No appreciable alterations in arterial blood pressure have been noted in human subjects after similar dosages. Cardiac output or coronary blood flow studies have not been made. Flushing has been noticed in only 4 patients receiving dibutoline.

**Clinical Observations.** Dibutoline has been employed as the sole therapeutic agent or as an adjuvant in treatment of the diseases listed below.

**Diseases of the Gastrointestinal Tract.**

1. *Colonic Spasm.* Nineteen cases of so-called functional spastic colon have received dibutoline in doses of 10 to 20 mg. subcutaneously as the sole therapy. Complete relief of their pain was afforded to all in from 1 to 10 minutes. The duration of relief varied greatly, in some instances lasting for several weeks and in others for 2 or 3 hours. One patient required 10 mg. every 4 hours day and night for several weeks. Another, was admitted to the hospital because of his severe colicky abdominal pain plus the presence of a 3 cm. hard, movable mass in the left, lower abdominal quadrant; X-ray diagnosis of this lesion was an obstructive, intraluminal growth of the sigmoid, probably malignant. He was given 10 cc. of dibutoline subcutaneously and after 90 seconds the patient experienced a dryness of the mouth followed in 2½ minutes by cessation of the pain and disappearance of the mass as determined by abdominal palpation; the latter observation was confirmed by a barium enema X-ray study.

2. *Diverticulitis of the Colon.* The abdominal pain associated with diver-

ticulitis has been relieved in all of 3 patients treated with dibutoline. Maintenance of freedom from abdominal pain was accomplished by using the usual 10-mg. dose 3 to 8 times daily.

3. *Chronic, Non-specific, Ulcerative Colitis.* Dibutoline has proved an important adjuvant in the treatment of all 6 cases of chronic ulcerative colitis in which it has been tried. It assists both in controlling the abdominal discomfort and in lessening the frequency of defecation. In one case 10 mg. of dibutoline given thrice daily was more effective than atropine gr. 1/50, administered at like intervals, in alleviating the abdominal pain and lessening the number of stools. In still another patient 20 mg. of dibutoline injected every 3 hours resulted in a stool-free period of 11 hours as contrasted to passage of 5 stools during an equal period when given powdered opium gr. iii orally every 3 hours over a 2-day period.

4. *Acute Gastroenteritis.* Fifteen cases of acute, severe gastroenteritis of undetermined etiology were treated with dibutoline in the usual 10-mg. subcutaneous doses repeated every 2 to 3 hours when necessary. Cessation of the vomiting and colicky pain resulted, as well as lessening of the frequency of defecation.

5. *Regional Enteritis.* Colicky pain associated with 1 case of chronic regional enteritis with external fistula formation was relieved by injection of 10 mg. of dibutoline 4 times daily.

6. *Pylorospasm Associated with Duodenal Ulcer.* In all 24 cases of typical pylorospastic pain associated with X-ray proven duodenal ulceration treated with dibutoline in 10 mg. doses complete relief was afforded; this alleviation of pain persisted for from 2 to 24 hours after a single injection and occurred in from 2 to 10 minutes after the injection.

Case Report. Case 1. A typical case

summary: A 47-year-old male was admitted to the hospital because of persistent, severe cramp-like pain in the epigastrium. He had been under treatment for recurrent duodenal ulcer for about 20 years. X-ray revealed a large crater in a spastic scarred duodenal bulb. Dibutoline, 10 mg. 4 times daily, afforded complete relief. Pain returned if a dose was omitted; atropine sulfate gr. 1/50 gave only partial relief.

7. *Functional Pylorospasm.* Ten patients with epigastric pain and vomiting with no demonstrable gastric or duodenal lesions were relieved by 10-mg. doses of dibutoline. Included in this group were 3 patients who had abdominal malignancies and whose nausea was adequately controlled without the use of narcotics.

8. *Pylorospasm Associated with Chronic Antral Gastritis.* Frequent vomiting and feeling of epigastric fullness were adequately relieved in 2 patients with chronic antral gastritis when dibutoline was given in 10-mg. doses every 4 hours.

9. *Peptic Ulcer Pain.* The typical ulcer-type epigastric distress occurring when the stomach is empty was relieved in 2 to 5 minutes after the injection of 10 mg. of dibutoline in 10 patients with X-ray proven duodenal ulcer. Not all patients with ulcer pain were so relieved, however. Such relief has also been noted clinically after atropine therapy.

10. *Pyloric Obstruction Associated with Duodenal Ulcer.* Three cases of pyloric obstruction all exhibiting marked degrees of duodenal narrowing and crater formation by X-ray and complaining of a feeling of epigastric fullness and frequent vomiting were rendered asymptomatic after the institution of dibutoline therapy consisting of 10 to 15 mg. of the drug injected sub-

cutaneously from every 4 to 24 hours.

Case 2. A summary of a typical case follows: A 30-year-old male with a history of recurrent duodenal ulcer for 7 years complained of a marked sense of epigastric fullness and vomiting, 1 to 4 times per week, for 15 months. X-ray showed food residue in the stomach, 50% retention after 6 hours and a marked duodenal bulb deformity. Dibutoline, 15 mg., was injected once daily and within a few days the patient felt improved. The daily injections of the drug have continued for 8 months and during this time the patient has been asymptomatic, has not vomited once, has gained 15 pounds in weight and has required no other medication except dibutoline. X-ray examination done 2 months after beginning dibutoline revealed the duodenal bulb deformity but no delay in gastric emptying time.

11. *Tabetic Gastric Crisis.\** The nausea, vomiting and abdominal pain associated with 2 cases of lues of the central nervous system were treated with 10- and 15-mg. doses of dibutoline. If symptomatic relief was obtained, it was only slight and transient.

12. *Infantile Pyloric Stenosis.†* Prompt and spectacular relief from the food regurgitation present since birth plus gain of 7 ounces weight in 4 days was afforded an 8-week-old infant by administration of 3 mg. of dibutoline 10 minutes before each feeding. A subsequent surgical procedure revealed the hypertrophic pyloric sphincter. In 3 cases of infantile pyloric spasm subsequently observed, dibutoline was found to afford only slight or equivocal relief.

**Gastro-Intestinal X-ray Observations.** Observations on the effect of dibutoline have been carried out in connection with clinical radiological work on normal individuals and on patients. Cases selected included instances of long de-

\* For the excellent observations in these 2 cases we are indebted to Drs. E. E. Peters, J. Rodrigues and B. G. Clarke of the Chicago Intensive Treatment Center.

† We wish to express our appreciation to Drs. Harry Tarre, J. B. Richmond and B. G. Clarke of Cook County Hospital for data in this case.

lay in the opening of the pylorus, especially where the delay was accompanied by demonstrable spasm of the prepyloric zone for distances of from 2 to 5 centimeters. Cases were also chosen where in giving the opaque enema a high grade of spasm was encountered in the distal colon. The dose administered was always 1 cc. (10 mg.) subcutaneously.

Some difficulty in the assessment of the results should be noted. It is a matter of common observation among radiologists that one often finds the first swallow of barium traversing the stomach and without any appreciable delay immediately passing into the duodenal bulb; in other cases a delay occurs, with no barium passing through the pylorus. In the latter event, various things may happen. In the usual case it may be observed that when one of the peristaltic waves approaches to within 3 or 4 centimeters of the pylorus, the latter opens and the duodenal bulb fills, to remain filled or to contract almost immediately with onward passage of part or all of its opaque contents. This may occur after watching only 1 or 2 minutes, or after a longer vigil the observer's patience may be strained and he may try a little manipulation with the palpating spoon or the protected fingers under the screen to slip some of the barium from the ampulla through the pylorus into the duodenum. This massage-like maneuver may succeed but in other cases it seems to set up even more stubborn tightening of the pyloric sphincter, with no barium passing into the duodenum. In other cases the radiologist may draw a word-picture, more or less eloquent, of a savory meal being eaten under pleasant surroundings. In most cases the stomach almost immediately will begin active peristaltic waves and within a few seconds pass material into the duodenal bulb. But there are instances in which all of these maneuvers fail, and then

one must seek some further means of visualizing the duodenal bulb.

Ordinarily atropine sulfate has been employed, beginning with a dose of  $1/75$  of a grain. One of us (J.T.C.) once gave  $1/75$  of a grain of atropine sulfate to 1000 consecutive gastrointestinal cases 30 to 45 minutes before the barium meal study was commenced. This was done because of the relatively large number (10 to 15%) of gastroduodenal studies where re-examination was requested to eliminate as far as possible any influence of pylorospasm. No untoward effects were observed in any of these 1000 cases which included young and old of both sexes, but it was noted that unless the atropine sulfate was given to full physiological effect, sometimes requiring  $1/30$  of a grain, the antispasmodic benefits were not assured. It may be that the same is true of dibutoline, for we observed variations of its effects.

In otherwise normal individuals who were exhibiting pyloric spasm, dibutoline usually had the effect of relaxing the spasm; so that whereas up to the moment of making the intramuscular injection nothing had passed into the duodenal bulb or beyond, within 3 to 5 minutes after the injection the barium mixture passed readily and spontaneously into the duodenum.

Sometimes the effect is not so prompt. In one case, repeated observations over a period of fifteen minutes from 10:30 to 10:48 revealed that no appreciable amount of contrast material passed into the duodenal bulb (Fig. 2a). At 10:48 dibutoline was injected. At 10:57 the bulb was beginning to fill. By 11:18 it was well filled and barium was beginning to enter the jejunum (Fig. 2b). At 1:15 the stomach was just emptying its last traces and the distribution of barium through the small bowel was normal. There were, however, cases in which

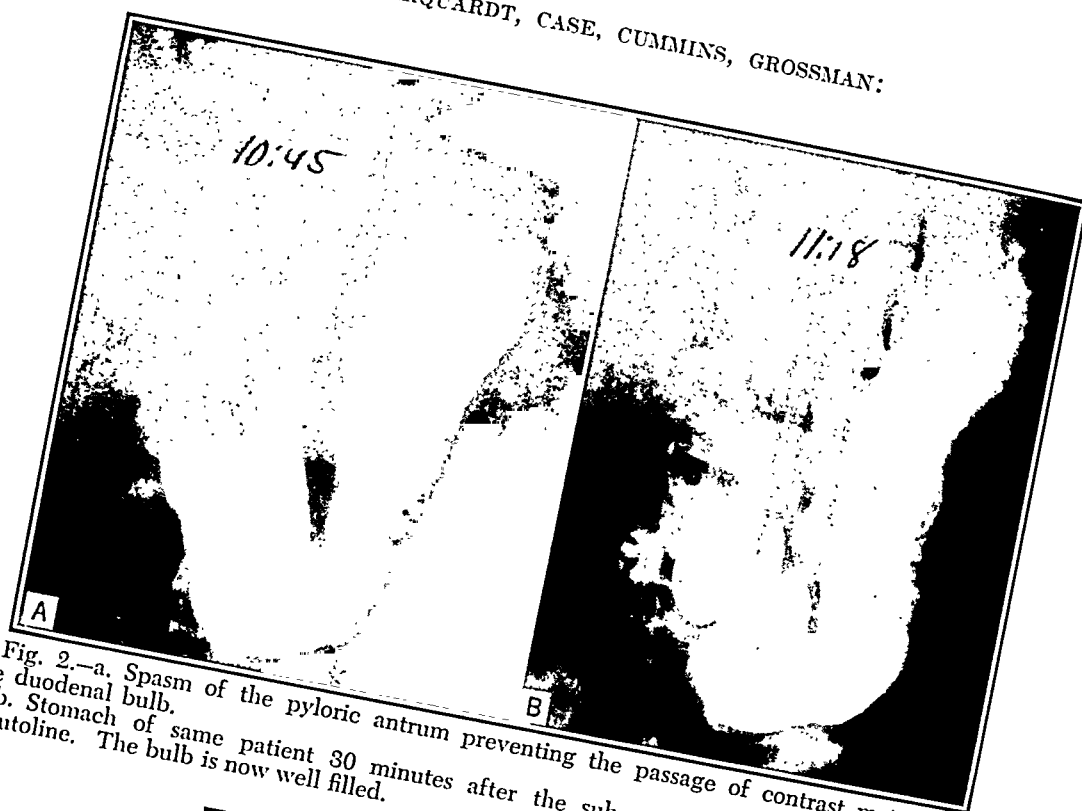


Fig. 2.—a. Spasm of the pyloric antrum preventing the passage of contrast material into the duodenal bulb.  
b. Stomach of same patient 30 minutes after the subcutaneous injection of 10 mg. of dibutoline. The bulb is now well filled.

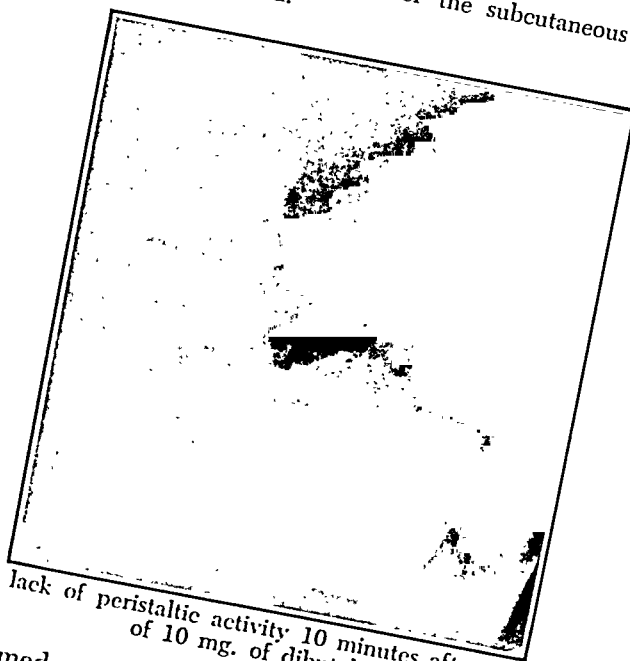


Fig. 3.—Atonicity and lack of peristaltic activity 10 minutes after the subcutaneous injection of 10 mg. of dibutoline.

the dibutoline seemed to have the opposite effect. In stomachs which showed no spasm or hyperperistalsis, the administration of dibutoline seemed to cause a slowing down of the motor process with almost complete cessation of its activity, this occurring within 30 minutes. This was noted for a period of about 1 hour, during which time there was a notable lack of passage of opaque materials into and along the small intestine. Then the

rate of transit of the opaque material became much more rapid and resembled the normal behavior.

In another case, during 20 minutes of observation nothing passed the pylorus, and we were unable by any maneuver to get anything into the duodenum. Dibutoline was injected and the bulb appeared spontaneously

much coaxing the patient had been persuaded to accept enough of the contrast enema to visualize the colon as far as the splenic flexure. He then rebelled and it became quite obvious that he could not take any more. He was studied in various projections to ascertain that there was no obstruction of any kind at the splenic flexure

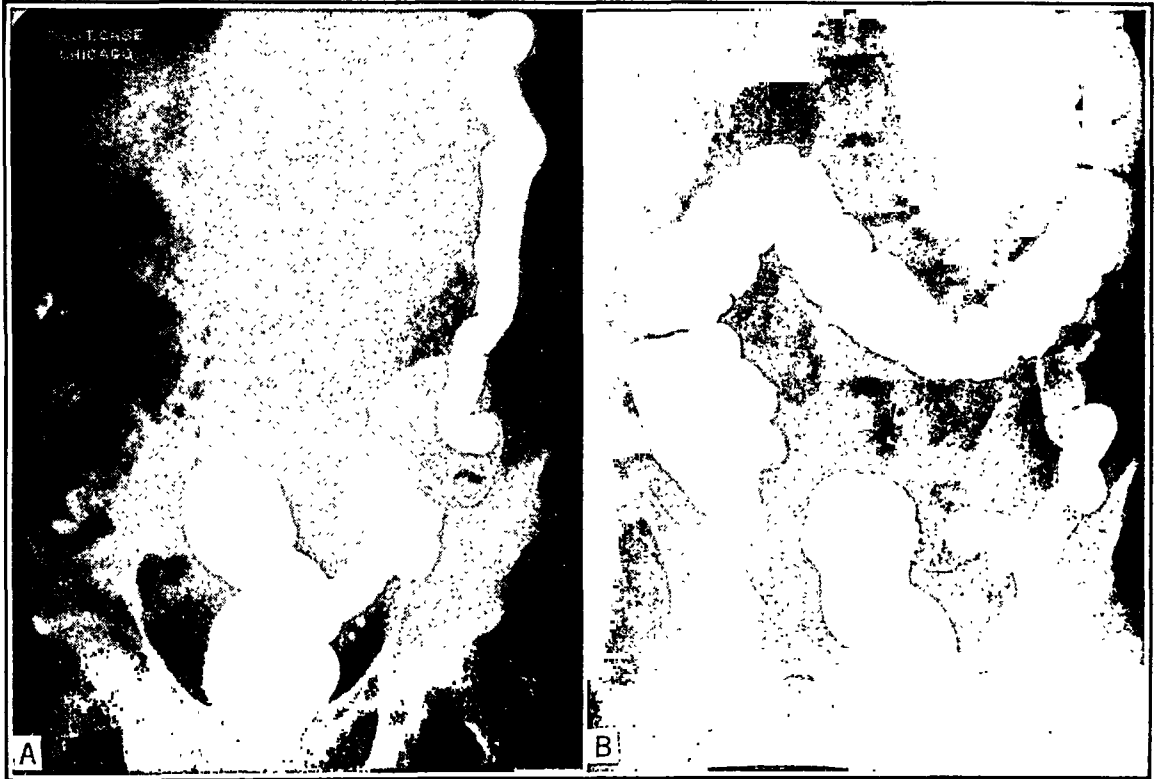


Fig. 4.—a. Incomplete filling of the colon due to generalized spasm.  
b. Colon of same patient 20 minutes after the subcutaneous injection of 10 mg. of dibutoline. Complete filling is now easily accomplished.

within 5 minutes but remained rather spastic and the stomach itself showed normal tonicity for about 5 minutes after which there supervened a period of atonicity, the stomach presenting instead a lack of peristaltic activity and the general aspect of gastrectasis (Fig. 3). Then there was a gradual resumption of normal peristaltic activity, so that within another half hour the active peristalsis had nearly emptied the stomach.

In another case, (Fig. 4a) the complete filling of the colon by the opaque enema was found impossible. After

to impede the progress of the barium through the colon. Obviously it was a case of intense colonic spasm. He was allowed to expel the enema, and returned to the table with the colon practically clear. Ten minutes after injection of dibutoline the enema was repeated. This time not the slightest difficulty was encountered in filling the entire colon over to the ileocecal valve (Fig. 4b).

**Diseases of the Biliary Tract.** 1. *Gallstone Colic.* Only 1 case of gallstone colic was treated with dibutoline. This patient was relieved completely



of pain 5 minutes after a 10-mg. injection of the drug. Atropine sulfate, gr. 1/75, had no effect in similar attacks in this patient.

2. *Biliary Dyskinesia*. A presumptive diagnosis of motor dysfunction of the gall bladder and sphincter of Oddi (not confirmed by visualization of the hepatic ducts during cholecystography) was made in 1 patient complaining of recurrent attacks of nausea, vomiting and right upper abdominal pain with interscapular radiation. Dibutoline in 10-mg. doses afforded this patient complete relief, while 1/50 grain of atropine sulfate did not.

**Diseases of the Genito-Urinary System.** 1. *Dysmenorrhea*. Relief of pain was afforded 10 patients with premenstrual cramps by 10 mg. of dibutoline. However, as had been our previous experience, little benefit was derived from dibutoline in 10 women experiencing pain after the onset of uterine bleeding. This observation lends credence to the hypothesis that premenstrual pain is due to spasm, while post-bleeding pain is not.

2. *Ureteral Colic Associated with Calculus*.\* The effectiveness of dibutoline in relieving the severe pain of ureteral colic in patients with stones has been variable. We believe the failure of treatment of some of these cases is due to inadequate dosage of the drug. Six cases of X-ray proven ureteral calculus were given 10 to 30 mg. of dibutoline and 3 of these were afforded complete relief of their pain without the supplementary use of narcotics or analgesics. The remaining 3 cases, however, required additional morphine sulfate for control of pain. In the successful cases pain was controlled by using 10 to 30 mg. of dibutoline every 3 to 8 hours; all 3 of these patients passed their stones spontaneously during treatment.

3. *Bladder Spasm following Cystoscopy and Transurethral Prostatic Resection*. With 1 exception, post-manipulative of post-operative pain after cystoscopy was controlled by dibutoline alone in 22 cases. No analgesics and no narcotics were necessary. The usual regimen consists of giving 10 to 20 mg. of the drug immediately before introduction of the cystoscope followed by a similar dose immediately after completion of the procedure.

4. *Cystitis*. The pain incident to infection of the urinary bladder was completely relieved by 10-mg. doses of dibutoline in 2 cases. In another like number of patients, however, sufficient relief was not afforded to warrant withholding analgesics.

5. *Suprapubic Prostatectomy*. Relief was given 3 post-operative prostatectomy patients by the use of 10 to 20 mg. of dibutoline every 2 to 3 hours. It was found, however, that the effect of dibutoline was enhanced by using a constant intravenous infusion of 5% ethyl alcohol solution. When these 2 medicaments were used simultaneously immediately after the operation, the relief afforded the patient was such that no opiates were necessary during the entire post-operative course.

**Side Effects.** The common side reactions to dibutoline treatment are dryness of the mouth and diminution of ocular accommodation. The dryness of the mouth usually lasts from 20 minutes to 1 hour and is considerably less distressing than that which follows atropine therapy. As was mentioned previously, we have not noted a significant tachycardia or alteration in the arterial blood pressure in any case in the doses of the drug used (3 to 30 mg.). Flushing of the skin has been observed in several patients. As much as 30 mg. have been injected subcutaneously with no other than the

\* We are indebted to the members of the Drs. V. J. O'Connor-K. Sokol G. U. service of Wesley Memorial Hospital, Chicago, for their cooperation in obtaining the results of dibutoline on urinary tract diseases.

effects noted above. One patient has received from 80 to 100 mg. of dibutoline daily in divided doses for as long as 2 months and has manifested only moderate dryness of the mouth and minimal visual disturbances. Three other patients have tolerated equally well 40 to 60 mg. per day for periods up to 3 months.

**Dosage.** The usual subcutaneous dose for adults is 10 mg. If no relief is obtained in 20 to 30 minutes, it has been customary to repeat the dose followed by injection of 10 mg. as needed symptomatically. The duration of action of the drug judged by clinical standards of patient comfort varied from 1 to 24 hours or longer. Occasionally in cases of severe spastic pain we have commenced treatment with 20-mg. dosage and repeated this amount as needed.

The drug has not been administered intravenously in human subjects. It has proved ineffective when given by mouth; no effect has been observed when as much as 1500 mg. has been taken orally.

**Clinical Value.** We believe that dibutoline has a place in the therapy of spastic disorders of the gastro-intestinal biliary and genito-urinary systems. Its usefulness is enhanced by intensity and promptness of its effect, a property not possessed by atropine. When almost immediate, powerful anti-spastic action is desired, dibutoline, on the basis of our experience, will accomplish this. The drug has also proved useful to the roentgenologist in combating spasm of the pylorus and antrum and the colon in gastro-intestinal X-ray visualization.

In many instances a single dose of

the drug provides relief for a period which far exceeds the duration of its pharmacological activity. This would indicate that in these cases once the spasm is relieved it does not recur immediately even though no drug is acting to prevent it. In the instances where this is not true the recurrence of pain may make quite frequent administration of the drug necessary; in extreme cases as often as every 2 hours. Inasmuch as the drug is only active by parenteral routes, this entails the inconvenience of repeated injections. The failure of the material to be active by the oral route seriously limits its use in ambulatory patients in whom it would otherwise be indicated.

**Summary.** Dibutoline, possessing both a smooth muscle inhibiting and an anti-acetylcholine action, has been employed as the sole therapeutic agent or as an adjuvant in the treatment of smooth muscle spasm associated with 12 types of disorders of the gastro-intestinal tract, 2 of the biliary tract and 5 of the genito-urinary system. The results have been most favorable with the exception of the treatment of gastric crisis associated with tabes.

The drug has proved useful in combating spasm of the upper gastro-intestinal tract and the colon during the course of X-ray examination.

Side effects of dibutoline have been mainly moderate dryness of the mouth and slight diminution of ocular accommodation following the usual 10- to 20-mg. subcutaneous dosage.

The drug has proved exceedingly useful when a prompt, powerful anti-spasmodic agent is indicated. The short duration of its action and its ineffectiveness orally limit its usefulness.

**Addendum:** Since submitting this report for publication, we have used dibutoline in the treatment of about 3 times as many cases of spasm as described herein with comparable results.

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# PROGRESS OF MEDICAL SCIENCE

## SURGERY

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## PROGRESS AND DEVELOPMENT OF ANESTHESIA IN THE UNITED STATES

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THE importance of the discovery of anesthesia for the relief of pain during surgical procedures is universally recognized as one of the major advances in surgery. Without anesthesia, surgery would be limited indeed. It is not the purpose of this paper to review the differences in surgery of the preanesthetic period with that of today. A discussion of the progress and development of anesthesia, however, must take into account the advances that have been made in this field not only in the development of drugs, but in the opportunities for training of personnel and the development of anesthetic agents and techniques. That in recent years there has been improvement in anesthesia is a well accepted fact; that progress is continuing in the field of anesthesia is evident and there appears to be still room for improvement even without the addition of new drugs. The final index of progress must be judged by whether an ever increasing number

of patients receives better and safer anesthetic management not just next year, but for years to come. It is important, therefore, to discuss the subject of anesthesia not only in relation to drugs and methods of procedure, but also in relation to the development of personnel.

The development in the management of pain relief for surgery may be arbitrarily divided into 3 periods. First, the latter half of the nineteenth century after 1846; second, the first quarter of this century; and third, from the end of the first quarter of this century to the present time.

The period immediately following Morton's successful demonstration of ether anesthesia was notable for the rapidity of acceptance of this new procedure. Thus, relief of pain and the horror of surgery was hailed as a turning point in surgical treatment. In those early days, surgeons were recognized because of their ability and judg-

ment and not by their tools, but there was no such recognition for the administrator of anesthesia. The controversy about prior rights in the use of ether as an anesthetic agent caused much conflict but no leader in the training of the anesthetist or an evaluation of the effects of anesthesia was forthcoming. It is regrettable that under such a state of affairs the progress and development of anesthesia was slow in America. Fortunately, with physicians following the influence and prestige of John Snow<sup>28,39</sup> in England, there were many contributions from that country, and his work was frequently quoted in American literature<sup>17,64,66,71</sup>.

We owe much to the dentists who became interested in anesthesia during the early period; they were mainly responsible for the early use of nitrous oxide and apparatus for its administration. Both Morton and Wells were dentists and this, no doubt, prompted the interest of others in their profession to take up anesthesia. There was no infiltration anesthesia then and restorative dentistry did not save as many teeth from extraction as does present-day dental care.

The drugs introduced and their methods of administration that originated during this first half century are of paramount importance and most of them are still in use; the same is true of the technics used at the end of this period, with some improvements.

Fortunately fate, plus Morton's persistence, determined that ether should be the first inhalation drug. Ether has many desirable properties as attested by its present-day use. The importance of this drug in the first century of anesthetic development is probably generally underestimated. It has been administered to millions of patients under every possible circumstance as to the operation, surgeon and administrator. We do not know how many anesthetic deaths have resulted from its use, and if we did, one could not judge

how well it was administered or how many more deaths might have occurred with another drug. The fact that it is still widely used for anesthesia is good evidence of its value.

Wells had been working with nitrous oxide to produce pain relief as early as 1844, but had not succeeded in convincing anyone of sufficient professional standing to have the idea accepted. This drug has a very low potency and is the only inhalation drug used that is not a hydrocarbon. In spite of the lack of potency, nitrous oxide is very widely used for induction of anesthesia and used with more potent inhalation and with nonvolatile drugs. Throughout the many changes in anesthesia, nitrous oxide continues to maintain some usefulness in nearly every operating room in this country.

Simpson's advocacy of chloroform in 1847 was of importance and it was widely used in this country only during this early period. Its one dangerous property, namely its propensity to disturb cardiac function if not administered with extreme care, still makes it unsafe for common use. It was used extensively in this country during this period and most writers recognized that it was not as safe as ether, particularly for the many unskilled individuals who were administering anesthesia<sup>4,63</sup>.

The use of ethyl chloride was perhaps of less importance but it is still used for inhalation anesthesia; Snow is supposed to have used it in 1851<sup>38</sup>. Rice says it was first used by Heyfelder in 1848 but never extensively until 1895, when a more purified drug was available<sup>56</sup>. The introduction of the use of oxygen with nitrous oxide by Andrews<sup>5</sup> was a valuable contribution. Snow used amylene and reported some 238 administrations, but it was not used by others as far as is known and is only of historical interest<sup>38</sup>.

The use of nonvolatile drugs, by mouth, to relieve pain is centuries old

but the administration of morphine, subcutaneously and intravenously, was made possible by the invention of the hollow needle by Wood in 1853. This needle with the proper syringe set the field for local and regional anesthesia.

In 1860, Albert Nieman<sup>39</sup>, of Germany, isolated the alkaloid cocaine in crystalline form and reported the numbing effect on the tongue. Corning experimented with spinal anesthesia and it was accomplished in humans at the end of the century by Bier<sup>10</sup> of Germany. Matas<sup>44</sup> was one of the first to work on this problem in this country. The topical use of cocaine in the eye was introduced by Koller<sup>39</sup> in 1884. The injection of nerves and tissues with cocaine to produce local and regional anesthesia was performed near the end of this period by Cushing and Halstead<sup>39</sup>, and also by Crile as reported by Matas<sup>46</sup>.

Apparatus for the administration of inhalation anesthesia was well on the way to furnish a background for later development. Oxygen and nitrous oxide were compressed in metal cylinders. The principle of rebreathing volatile drugs was employed, though not highly developed. Squibb<sup>62</sup> and Prince<sup>55</sup> advocated allowing adequate air with ether and this culminated in real open-drop technic.

The practice of keeping records during anesthesia was started by Codman and Cushing<sup>8</sup>. Blood pressures were taken with the Riva-Rocci sphygmomanometer as introduced into this country by Cushing<sup>30</sup>. These pressures were recorded on a graphic record before, during and after operation. However, it remained for a later publication<sup>50</sup> to convince the anesthetist of the value of such records.

The second period, 1900 to 1925, was filled with tremendous advances in all scientific fields, including anesthesia. While the development and improvement in technics and practices from the previous period were of signal im-

portance, many new anesthetic agents were discovered.

The most important class of drugs introduced was the synthetic nonvolatile cocaine substitutes to be used for blocking nerve impulses, commonly called local, regional and spinal anesthesia. The first of these to be used extensively was stovaine, synthesized in 1903. In 1904, Einhorn synthesized procaine which replaced stovaine and remains one of the most widely used drugs for conduction anesthesia. The use of local as well as spinal anesthesia played an important part in interesting the profession in anesthesia; it gave opportunity and necessity for surgeons to become concerned with this field. Many minor surgical procedures could be performed with local infiltration much more safely than with poorly administered general anesthesia. Epinephrine, discovered in 1897<sup>1</sup>, came into use as a vasoconstrictor in combination with local anesthesia in this period. Ephedrine, described as a vasopressor drug by Chen and Schmidt<sup>14</sup>, was later employed in conjunction with spinal anesthesia.

Ethylene, introduced by Luckhardt<sup>42</sup>, was the only important addition to the inhalation anesthetics during this period. Its discovery stimulated further search for inhalation drugs.

The introduction of new technics also received a large amount of attention. Herb<sup>33</sup> states that Prince advocated using an open mask for ether and this method was widely used in this period as an improvement over the use of the closed cone. Prince modified the Esmarch mask to make the best open ether mask<sup>54</sup>. The intralaryngeal insufflation for open chest was described by Matas<sup>45</sup>. Kuhn's intratracheal tube was reported by Hazelhurst<sup>31</sup>. The work of Meltzer and Auer<sup>47</sup> led to the development of intratracheal insufflation<sup>10</sup>, which, in turn, was a forerunner of present-day endotracheal airways, which in this country was described by

Janeway<sup>30</sup> in 1913. This technic was developed largely by the English anesthetists, Magill and Rowbotham<sup>58,59</sup>. The latter was a very important contribution because the most troublesome and dangerous complication of all general anesthesia is respiratory obstruction. The use of the endotracheal airway, which consists of a tube of sufficient size to permit breathing through its lumen, has been a most valuable feature in rendering safer and better anesthesia with greater convenience to the surgeon. The history and development of this type of airway is very capably presented by Gillespie<sup>24</sup>.

Spinal anesthesia was well understood and used by some during this period but not widely. This work, interestingly enough, at the early stages, was done mostly by surgeons; one of the outstanding being W. W. Babcock.<sup>7</sup> The professional anesthetists' time probably was consumed administering inhalation anesthesia or perhaps they were not interested in spinal anesthesia at that time.

Inhalation apparatus was improved. Rebreathing technic was worked out carefully by Gatch<sup>23</sup> McKesson developed the intermittent flow valve<sup>48</sup>. The carbon dioxide absorption technic was introduced as a laboratory procedure by Jackson<sup>35</sup> and for clinical anesthesia by Waters<sup>67</sup>. However, the introduction of this apparatus did not simplify anesthesia but actually added responsibility for the anesthetist, because the patient must live on the atmosphere made by the anesthetist in contrast to the open drop, where ether is added to atmospheric air breathed by the patient. In spite of the high oxygen concentration possible with ether and the carbon dioxide absorption technic, there is a respiratory hazard of inadequate pulmonary ventilation that may be overlooked because of the good color of the blood and often absence of any marked changes in circulation until late in the sequence of events that

may lead to severe complications. The use of an artificial atmosphere may be hazardous therefore, if one does not have a proper understanding of physiology of respiration.

McKesson's report is both an excellent discussion of the physiology of circulation during anesthesia, and a demonstration of the importance of keeping a graphic record of the patient's condition. It so stimulated others<sup>49,50</sup> that by the end of this period adequate records were kept by most professional anesthetists. Further development of this phase of anesthesia came in the next period as part of the improved teaching program.

A summary of the progress in anesthesia during this period is striking for the many advances in the knowledge of drugs, technics and the management of the patient. Spinal, nerve block and local anesthesia were highly developed. Inhalation methods were improved and at the end of the period the carbon dioxide absorption technic was in practical use. The use of endotracheal airways was well established and found increased use in the next period.

During the more recent period (1925-48), many new drugs were added without discarding the old ones, but Squibb's statement is still as true as it was in 1871; "Time, that tries all things, has disposed of many of the issues which arose in the early application of anaesthesia, but has entirely failed in producing that universally applicable anaesthetic—that philosopher's stone for which the alchemists of the profession still vainly search—namely, an agent which shall be potent, but potent only for good. This physical impossibility seems to be to the medical profession what perpetual motion is to mechanics, and time wears away such heresies very slowly. It would, doubtless, be better for the profession and for mankind if the anaesthetics already known were better studied in relation

to their special adaptations, and were applied with a more wise discrimination"<sup>61</sup>.

There had been interest in intravenous administration of anesthesia for some years and, with the introduction of pentothal sodium, this type of anesthesia became very useful. It has been well discussed by Adams<sup>2</sup>. It has the advantage of producing unconsciousness rapidly and pleasantly with a minimum of after effects that are remembered by the patient. Its limitations and disadvantages in producing good surgical anesthesia if used alone are now recognized. It is rarely used as the only drug where relaxation, prolonged time and debilitated patients are involved, because it does not block certain spinal reflexes with the amount of depression tolerated under these conditions. The ease of intravenous injection may lead unqualified administrators to misuse the drug. The failure to remember that the production of unconsciousness with any drug places severe responsibility on the administrator may lead to trouble, especially in office practice and when done by those not familiar with preventing and treating the possible complications of this state. The discovery by Griffith<sup>26</sup> that curare preparations could be used and controlled in producing relaxation, and its further introduction into anesthetic practice by Cullen<sup>15</sup>, has also been a helpful adjunct, through the intravenous route of administration. As with other drugs, one can only estimate the required dosage and an overdose must be treated by artificial pulmonary ventilation. Its proper use produces good muscular relaxation with lesser concentration of other drugs. It has also been employed to control convulsions and muscle "spasm".

The intravenous use of procaine hydrochloride to produce analgesia for labor pain and parturition was used by Allen and Crossman<sup>1</sup>. However the

hazard of convulsions occurred often enough to discourage its widespread use. Burstein<sup>13</sup> used intermittent injections of procaine to treat severe cardiac depression or irregularities during cardiac and pulmonary surgery. Fraser<sup>20</sup> has reported the use of small amounts of procaine intravenously as an adjunct to general anesthesia, particularly to prevent cardiac arrhythmia. Bittrick<sup>11</sup> reported the use of large doses of procaine during intrathoracic operations. The reviewer<sup>65</sup> has been studying the use of rather large doses of procaine given intravenously in conjunction with other drugs that produce general anesthesia. Procaine hydrochloride 1% is given continuously in 5% glucose at a rate of 2 to 10 cc. per minute. It has been tried with several drugs; the most satisfactory has been a combination of pentothal induction followed by intravenous procaine and continuous flow of nitrous oxide and oxygen. If relaxation is necessary a curare preparation is used. The study has not been completed but some impressions have been formed: the procaine does not accumulate in the body as in the case of barbiturates; the only effect remaining after its flow is discontinued is pain relief, and consciousness returns rapidly; because of pain relief patients are not irrational but very clear mentally on recovery; the cough reflex is markedly depressed even in light anesthesia so that patients tolerate an endotracheal airway well; patients with toxic thyroid disease are benefited by procaine in that they have fewer pulse and pressure changes during operation and appear to be less disturbed during the postoperative period. These findings during anesthesia and operation have given reason to believe that intravenous procaine properly controlled might be efficient in treating thyroid crises. Postoperative pain relief is quite variable, ranging from 30 minutes to several hours. Vagovagal reflexes are depressed and per-

haps other undesirable activities of the autonomic nervous system are depressed or eliminated. This use of procaine should not be confused with the therapeutic use described by Peterson<sup>51</sup>, because these large doses require more careful observation and control; they are not without danger the same as any other drug used in the degree necessary to produce surgical anesthesia.

The synthetic cocaine substitutes metycaine, pontocaine, nupercaine, monocaine and intracaine have been given an extensive clinical trail and compared with the old standby procaine hydrochloride. Anesthesiologists trained in their use, limitations and dangers have found the longer acting ones such as pontocaine and nupercaine of value because of this duration of action, if at the same time proper precautions are being taken against excessive circulatory depression and respiratory paralysis. Lundy<sup>43</sup> has discussed these drugs and the technics in detail.

Two inhalation anesthetic drugs, divinyl ether and cyclopropane, have been accepted for clinical use since 1925. Ravdin et al.<sup>26</sup>, reported a careful laboratory and clinical study of divinyl ether. This drug produced unconsciousness rapidly and was less irritating to inhale than ethyl ether. It is chiefly used for very short operative procedures or for induction before ether anesthesia. It is not toxic to the heart, but is toxic to the liver and kidneys if given for prolonged anesthesia. It produces rather marked salivation in patients not given belladonna drugs. Cyclopropane was also studied extensively before being released for general use by Waters and his colleagues<sup>69,70, a, c, d, e, f</sup>. It was found to produce a pleasant induction and ample oxygen could be used because of its potency producing anesthesia in 10 to 30% concentrations in the inhaled atmosphere. It was best used with the carbon dioxide absorption technic.

Undesirable post-anesthetic complications such as nausea were much less than with ether. On the other hand this drug does not depress the activity of the autonomic system as in case of ether, and certain undesirable reflexes are not well obtunded by it in ordinary concentrations such as the laryngeal and vagal reflexes. While it does not depress the circulatory system, it may disturb the automaticity of the heart with resultant cardiac arrhythmia. It cannot be safely and economically administered by all methods as in the case of ether. In order to take advantage of its desirable properties one needs to be skilled in its administration.

The introduction of these two drugs illustrates the highest degree of precaution taken before they were released for general use and displays good cooperation on the part of the manufacturer and research worker during the study and clinical trial period.

Recently a similar study lasting for a period of 8 years has been reported in relation to chloroform, with careful laboratory and clinical controls<sup>70 b, c, e, 52</sup>. The cardiac effects of chloroform and cyclopropane were studied on dogs. Liver and kidney function were followed carefully on many patients receiving chloroform, cyclopropane and ether. Electrocardiographic records were taken on many hundreds of cases. In brief, the tendency of chloroform to produce liver and kidney damage is not particularly different from the many other anesthetic drugs<sup>52</sup>. However, its danger lies in the all too frequent serious cardiac depression. There were no cardiac deaths in over a 1000 administrations but there were instances of cardiac arrest which were corrected by prompt and vigorous pulmonary inflation with oxygen<sup>70-a</sup>.

New technics and methods of administration, or re-introduction of old methods, have been of advantage. The Lemmon technic of continuous spinal



of patients as well as a much improved professional status for the anesthetist-ologist.

During the period immediately following the introduction of anesthesia the personnel involved in the administration of anesthetic agents was apparently not thought to be of much importance. In the case of the first public administration of ether, the surgeon was the key figure. Despite the fact that Morton conducted a demonstration which was obviously destined to change the course of surgery, to save lives and alleviate suffering, the remarks about the performance which we remember were those of the surgeon. If Warren's remark, "Gentlemen, this is no humbug", established the respectability of anesthesia itself, it did nothing to encourage physicians to become anesthetists. Actually data concerning individuals interested in the administration of anesthetic drugs in this early period are hard to find and more difficult to evaluate. Most of the innovations were introduced by surgeons who naturally were much concerned with anesthesia. As to the administrators of anesthesia one finds lamentations in the literature concerning the neglect of this aspect of anesthesia. In 1860, an editorial states, "The delicate and most responsible task of administering the agent is usually committed to a junior physician who has no knowledge whatsoever of the nature of his duties; he knows nothing of the different stages through which the patient is to pass or the value of the symptoms which appear during the administration".<sup>17</sup> In the same year Squibb<sup>18</sup> wrote concerning the importance of the skill and experience of the administrator. Inspired by John Snow, English physicians took over the administration of anesthesia in large measure and it was developed and treated as a branch of the practice of medicine. There was no such recognition of professional an-

esthesia<sup>19</sup> and its auxiliary continuous caudal anesthesia, introduced by Hingson (See Edwards and Hingson<sup>18</sup>), have finally settled into their respective usefulness after waves of popularity. They have added increased technical requirements and the advantage of lending control to spinal anesthesia that is of particular value in some cases, this control involving both level and duration of anesthesia. The idea of using a vasoconstrictor drug in the anesthetic solution in spinal anesthesia was revived and is now being tried widely<sup>20</sup> to prolong the time of analgesia of procaine and pontocaine. The effect of these drugs given intrathecally has not been found to make much difference in the blood pressure according to clinical and laboratory work done by Henderson<sup>21</sup>.

Along with operative surgery, anesthesia has benefited much by the application of knowledge of human physiology. Even within the reviewer's experience there has been a marked improvement in preoperative care of patients. Proper use of parenteral fluids, electrolytes and blood have been highly beneficial. How one used to dread anesthetizing patients with intestinal obstruction and marked abdominal distention! With long tube decompression introduced by Abbott and Johnston<sup>22</sup> the anesthesia problem and hazard has been reduced. The modern operating room usually has cross-matched blood ready for every procedure that may be accompanied by considerable blood loss during operation. Blood is replaced as lost to prevent circulatory depression and shock is usually not allowed to develop.

The third period has brought new drugs, new techniques, new teaching methods, new fields in therapy outside the operating theater, a new name "anesthesiologist" to replace the old term "anesthetist", new problems in economics, and we believe much improved clinical anesthesia to a larger number

esthesia in the United States at that time. A few men were engaged in clinical anesthesia at the turn of the century and their numbers increased in the next period. Apparently the task of administering anesthesia was the least desirable and was assigned, all too often, to the "low man on the totem pole". The importance of the administrator of anesthesia was not recognized, it provided very little remuneration, and therefore few were found who were willing to devote the majority of their energy and interest to this phase of surgery.

The practice of utilizing an apprentice or intern for the administration of anesthesia until he was permitted to carry on what was considered more interesting activity has persisted in many places until recently. However, as might be expected, the dependability of such personnel for anesthesia caused frequent difficulties for the surgeon and gradually gave impetus to the development of personnel for anesthesia along two lines: One, the employment of physicians who spent the major portion of their time administering the anesthesia, and two, the employment of specially trained graduate nurses for this purpose.

Galloway<sup>21</sup>, writing at the end of the century, pointed out that for the most part anesthesia was poorly taught to medical students. After a lecture from the surgeon on anesthesia, they were expected to be able to administer anesthetic agents without further supervision and perhaps no period of observation. In discussing the relationship of the "anaesthetizer" to the operating surgeon, he says, "To do his best work, the surgeon must not have the responsibility of the administration of the anesthetic on his mind; the anaesthetizer must have sufficient skill to keep the patient in the best possible condition to facilitate the operation." He also had a well advanced understanding of proper professional respect as shown

by his statement, "In private practice the surgeon or the family physician should introduce the anaesthetizer to the patient with the cheerful assurance that in this doctor's hands he need not have fear for his safety or comfort". In another publication, Galloway<sup>22</sup> discusses the need for a specialty of anesthesia and states his views on the importance of anesthesia, which are well ahead of the beliefs and practices of many other surgeons of his time. He made the following very interesting prophesy: "The anaesthetizer will have to make his own place in medicine; the profession will not make a place for him, and not until he has demonstrated the value of his services, will it concede him the recognition which the importance of his duties entitles him to occupy. He will be obliged to define his own rights, duties and privileges and he must not expect that his own estimate of the importance of his position will be conceded without opposition". This is an amazing prediction of the steps, trials and tribulations that the specialty and its active members have passed through since Galloway offered this information in 1899.

The present director of Anesthesiology at Flower Hospital, New York City, D. E. Brace, is in charge of the oldest department of anesthesia organized and staffed by physicians, in this country. In 1899, the late T. S. Buchanan was appointed attending anesthetist at Flower Hospital in New York. As far as I have been able to ascertain, this was the first Department of Anesthesia in a hospital and medical school with physicians designated as anesthetists. Buchanan was apparently the first professor of anesthesia when he was appointed to the Chair of Anesthesia, established at Flower School of Medicine in 1905<sup>12</sup>. The Hahnemann Hospital and Medical School in Philadelphia started a department of anesthesia about the same time and these departments have been staffed

entirely by professional anesthetists ever since their inception. Previous to this organization anesthesia was administered by physicians<sup>60</sup>. These institutions, as well as many others, have demonstrated that anesthesia can be conducted entirely by the profession without technical administrators. In 1898, Dr. T. L. Bennett<sup>9</sup>, one of the early pioneers in the practice of anesthesia in New York, was listed under the title of Anaesthetist and Instructor in Anaesthetics, Hospital for Ruptured and Crippled, New York.

Golden<sup>25</sup> has written at length discussing his difficulties in maintaining his independence as a consultant in anesthesia and collecting his fees directly from the patient. It seems to have been common practice after 1900, as well as before, for the surgeon to pay the anesthetist after collecting from the patient. This allowed the surgeon to fix the fee, make profit on it if he was not honest and was another irritating means of keeping the anesthetist subordinate.

There were many essays published concerning the status of anesthesia and anesthetists. Organized teaching was started in some medical schools. Robb<sup>57</sup> in 1909 recommended that a medical anesthetist hold a staff appointment in the medical school to teach anesthesia to medical students, both theoretical and practical. Long<sup>41</sup>, in 1915, declared anesthesia to be a full fledged specialty and also admitted that a problem still existed in this statement "If the administration of anesthesia were not looked upon as a trivial matter by the majority of surgeons and hospitals, and if the expert anesthetist were accorded the same recognition as a consultant, as are the men in all other specialties there would be no anesthesia problem for solution".

Improvement in personnel was the very important feature of the period from 1900 to 1925. This phase of development has been ably discussed by Waters<sup>68</sup>, and he has paid highest trib-

ute to F. H. McMechan for his years of capable organization and his stand for better anesthesia. The reviewer recommends all the publications presented at the Ether Centennial for reading as they cannot be improved upon for the phases which they cover<sup>6</sup>. There was a marked increase in the number of physicians directing their activities to anesthesia. The Long Island Society of Anesthetists was formed in New York in 1905; the first member, Erdman, is still living. This became the New York Society of Anesthetists and was later organized as the national organization (Gwathmey)<sup>20</sup>. With F. H. McMechan as editor, the Quarterly Supplement in Anesthesia was published in the American Journal of Surgery from 1914 to 1926. Also, Year Books in anesthesia were published in 2 volumes for 1915-16 and 1917-18. These journals contained many excellent publications by outstanding anesthetists and are recommended reading.

During this time the nurses employed by hospitals were taking an important part in anesthesia, namely, that of getting "today's work" done, which, after all, is very important. It was never intended that they would bring about scientific advances in the specialty; nor was it intended that they would delay or prevent progress; so, if the latter has happened, it was indirect and unintentional. The question arises how will this large group of nurse anesthetists fit into the next period where we can already anticipate marked changes in personnel administering anesthesia. Actually, with the rapid growth of the country with increases in population there was need for all the physicians and nurses available for any or all branches of surgery. There was ample room for an increase in numbers of professional anesthetists without changing the entire personnel problem, except for constant improvements in the quality of the work.

The specialty of anesthesia, how-

ever, was not widely recognized or accepted by the medical profession until recently. Some communities enjoyed the services of anesthetists who were doctors of medicine and who devoted their full time to anesthesia; other areas had no such service. Incident to the increase in number of surgical procedures there was a marked increase in the number of nurses administering anesthesia. The remuneration was better than for other types of nursing and the demand for someone to do anesthesia was great. Confronted with this problem, many hospitals formed their own department and regarded the administration of anesthesia as a hospital service instead of a professional one. This resulted in many physicians losing their interest in anesthesia, particularly those who had spent but a part of their time and interest in the field. In larger hospitals and medical centers physicians stopped administering anesthesia unless they wished to continue as full time specialists. Some physicians accepted this system, working for a salary and doing contract practice of medicine. In some hospitals where physicians capable of administering anesthesia were available, it was not included as a hospital service but the anesthetist worked on a fee basis. Even at the end of the first quarter of the century very few medical schools had proper teaching facilities in anesthesia for students. Medical students from most schools saw anesthesia administered by nurses and had their practical training, if any, from nurses. It is little wonder that very few thought of choosing such a field for their life's work. Fortunately, some students encountered professional anesthetists and became interested in the specialty. In this period most surgeons' experience with physicians administering anesthesia was with those who had no schooling in the subject, and whose skill, in many instances, was limited. A fair number of physicians had become very proficient in

using some anesthetic drugs and there was a small number who spent nearly all their time administering anesthesia and could rightly be classed as specialists. An organized system of teaching and dissemination of information was generally lacking. Therein lay the weakness of the specialty. What good to have so much knowledge and facts which were known but used by so few? The importance of anesthesia was recognized by some but many seemed to think these new features could be carried on readily by non-medical personnel. The specialty was not sufficiently supported financially or professionally to attract enough physicians to its fold. The only good feature about this was that very few entered the specialty who were not interested enthusiasts, whose influence was to be felt in the next period.

Though our leaders and teachers are not entirely satisfied, they have accomplished a very good job during the period from 1925 to 1948. One measure of professional activity of a group is its organizations and publications. The activity of organizations to improve anesthesia has been continued and increased during this period. Such organizations are common to all specialties as are the resulting meetings and publications for the specialty and the profession.

The New York Society of Anesthetists, organized in 1912, became the American Society of Anesthetists in 1935. With a recognized national organization, steps were taken to obtain an American Certifying Board. This was accomplished in 1937 through the cooperation of the American Board of Surgery, which permitted Anesthesiology to be affiliated with the surgical board; in 1941 this was changed so that anesthesiology had a separate board. In 1947, steps were taken to make each State Society of Anesthesiologists a component of the American Society of Anesthesiologists with a new system of representation from the en-

tire country and Canada. Canadian anesthesiologists have always carried on a welcome and active part in the organizations and progress of anesthesia of the United States. Paul Wood deserves credit as the leader, adviser and worker in the organization of anesthesiology during this era. A tribute has been paid him by Waters<sup>68</sup> in his discussion of progress during this time.

The most important progress in anesthesia during the last quarter century has been the improvement in teaching methods with the results of a marked increase in the number of qualified medical anesthetists. Residencies and fellowships were offered for one to three years in institutions where qualified teachers, in both theory and clinical anesthesia, had departments of anesthesia. At first, most of these were sub-sections of surgery. Before this time, the apprenticeship system had been used and a few very short courses—one to two weeks—were offered in some centers. Attendance at meetings and reading of publications, plus one's ability to learn things by oneself, determined the degree of perfection attained. The new idea of teaching anesthesia on a scientific basis, with experience under careful supervision, as during a residency, was a sound one. At the present time nearly every medical school has a teaching department in anesthesiology, as do many of the larger clinics. A teaching institution can readily get "today's work" done entirely with properly supervised students, interns and residents, with a proper teaching staff.

At the present time there is discussion regarding whether or not nurses should administer anesthesia and most of this is based on a misunderstanding of the principles involved as well as a fear of dictation by groups interested in anesthesia. Actually the nurse who administers an anesthetic is presumed to act under the guidance of a doctor of medicine, usually a surgeon. Since

the nurse is an agent of the surgeon in such instances, it is the surgeon who is responsible for the acts of the nurse as anesthetist. The lay superintendent of a hospital cannot assume this responsibility any more than he can assume the responsibility for the operative procedure. Unfortunately, at the present time there are not sufficient medically trained individuals who are interested and trained in anesthesia to provide the personnel necessary to carry on the present day to day work. Accordingly, it is necessary that technicians be employed as they have been in the past in those communities and institutions for which qualified anesthesiologists are not available. This does not mean that anesthesia in such institutions will not be so good as in the past, but rather that it will not progress as it should in the future. In many communities nurse anesthetists have fulfilled the obvious needs for anesthesia required by many surgeons and will likely continue to do so.

The responsibility for the administration of anesthesia is not to be lightly considered. He who administers a drug to produce surgical anesthesia, administers the most potent depressant drugs to the most extreme degree of anyone practicing medicine. Instead of hours or days to note the effects of drugs, as in many phases of medicine, the effect will and must occur in minutes or seconds in surgical anesthesia. The extreme degree of depression produced cannot be safely done with a fixed dosage of any drug. Each must be administered as required by each patient for the desired effect when that can be accomplished without endangering the patient's life. This makes it nearly impossible to order the proper dose beforehand; all of which means that the administrator must have ability to vary the dosage and other factors for each patient and each type of operation. To this must be added knowledge and understanding of pre-existing

diseases and abnormal physiology in many patients that need surgical treatment. The results produced in the disturbance of physiology of respiration and circulation during anesthesia are very unpredictable, much more so than the results from an average operation. Difficulties frequently arise which require immediate recognition, diagnosis and correction to avoid delayed or immediate damage to the patient. This can be done by the anesthesiologist without interference with the surgeon's work or peace of mind. One finds the best of surgeons very grateful for this relief from responsibility even though they were able to get along before quite well by supervising the anesthesia carefully themselves. Then comes the situation of learning when mistakes are made; a professional anesthetist may make mistakes, but, if properly trained, he will learn not to repeat them. During his training period anesthesia will not be perfect but, properly supervised, it will be safe. Non-medical personnel are apt to repeat the same mistakes more frequently unless they have proper supervision.

The problem of teaching anesthesia to graduate and undergraduate students is a serious responsibility of medically trained individuals interested and trained in anesthesia. Technicians who are unfamiliar with physiology and pharmacology, as well as the responses of the individual to disease entities can do little in the way of supplying instruction to medically trained personnel. It is not likely that students will respect the individual who is not medically trained so far as medical subjects are concerned, and this includes anesthesia. Even in the case of anesthesia programs where there is a mixture of medically trained anesthesiologists and technicians, difficulties are present in relation to training of the anesthesiologist. The facilities of well organized departments of anesthesiology are taxed to the limit with

the important job of training qualified doctors of medicine and this, along with providing good anesthesia and contributing to the advancement of the field, is an important task. All communities are not of sufficient size to support an anesthetist who devotes full time to the subject. Such is likewise true in the case of other specialties. This problem has not been settled by the utilizing of technicians to carry out procedures in surgery or obstetrics. Trained anesthesiologists in smaller communities may carry on other types of practice as is common in the case of other specialties. Since it is now possible in most communities to practice anesthesiology on the same basis as consultants in other specialties, encouragement has been afforded to doctors of medicine to enter the field. The concept that the anesthesia consultant ought to have the same status as other consultants is reasonable and proper. Institutions which employ all others on the professional staff are the only ones which logically might expect to do so with the anesthesiologist.

In summary, anesthesia made little progress during the first period (1846-1900), but since 1900 there has been steady advance not only in the use of new agents and methods, but also in the matter of development of individuals highly skilled in the knowledge and technics of anesthesia. The specialties of anesthesia and surgery are closely allied. To be most effective the anesthesiologist and the surgeon must cooperate not only for the best interest of the patient but also for the advancement of both fields. Better anesthesia has permitted surgical procedures which would otherwise not be possible. The requirements of the surgeon for better anesthesia to extend his usefulness has been largely responsible for the increased demand for professional anesthetists and other advances in anesthesiology.

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# OPHTHALMOLOGY

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## THE OCULAR CHANGES ASSOCIATED WITH PHEOCHROMOCYTOMAS

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ONE of the curable types of vascular hypertension is that associated with the release of pressor substances into the blood in excess amounts by the tumors of chromaffin tissue called "pheochromocytoma", "paraganglioma", or "chromaffinoma". These tumors occur most frequently in the medulla of the adrenal gland, but they have also been found in various other locations. They can occur wherever there is chromaffin tissue in the body. Such tumors have been found in the retroperitoneal tissues, in the sympathetic ganglia along the aorta or the vena cava, in the carotid body, in the organ of Zuckerkandl at the bifurcation of the aorta, and 1 case<sup>21</sup> has been reported arising from the second thoracic ganglion. If the tumor is present in the adrenal medulla, it is then usually called a "pheochromocytoma", while those in other locations are designated "paraganglioma".

These adrenalin-producing tumors arise from the primitive sympathetic cells, the sympathogonia. These sympathogonia produce 2 kinds of cells in their development — the sympathetic ganglion cells and the endocrine cells. The latter are called pheochromocytes. They arise from the sympathogonia through the pheochromoblasts. The mature pheochromocytes are recognized easily in histologic preparations because of their affinity for chrome salts

which stain the cellular substance brown. These cells secrete adrenalin, the pressor substance, which is then discharged into the blood stream periodically, and sometimes continuously. When they are present in abnormally large numbers, as in neoplasm, they give rise to the syndrome which has come to be recognized as indicative of the presence of a chromaffinoma.

These tumors are nearly always benign histologically, even though they may cause the death of a patient by progressive elevation of blood pressure and subsequent damage to the arteriolar system. Baumgarten and Cantor<sup>4</sup> have aptly stated that chromaffinomata are benign anatomically but malignant physiologically. A small number of the reported cases have actually been malignant tumors histologically which had invaded the surrounding structures.

Pheochromocytomata are relatively rare tumors. The original description of this tumor was made by Fränkel<sup>22</sup> in 1886 when it was found in the adrenal gland of a patient who had come to autopsy. His report included a histologic description of the pheochromocytoma as well as a clinical history, physical examination and a report of the ocular fundus. Recognition as a clinical entity stems from the report of Labbé, Tinel and Doum-

er<sup>37</sup> in 1922. The first surgical removal with cure of the condition was accomplished by C. H. Mayo<sup>43</sup> in 1926. This was a retroperitoneal tumor in the region of the kidney and pancreas and was a typical pheochromocytoma. The patient is still alive and well. The first correct preoperative diagnosis followed by cure subsequent to operation was the case reported by Pincoffs<sup>52</sup> and Shipley<sup>59</sup> in 1929 where the tumor was found in the adrenal and had grown adherent to the vena cava. In 1944, MacKeith<sup>41</sup> found 165 case reports. Snyder and Vick<sup>60</sup> in a careful review of the literature up to 1945, were able to find a total of only 84 cases which they thought were proved chromaffinomas with convincing evidence of hyperadrenalinemia. Since then about 35 additional proved cases have appeared in the literature. The most complete review of the ocular changes associated with this condition was published by Bruce<sup>11</sup> in 1947. He analyzed 38 case reports from the literature and discussed in detail the ocular changes in 3 cases, which also are reported elsewhere by Snyder and Vick<sup>60</sup> and by Goldenberg, Snyder and Aronow<sup>24</sup>.

The so-called "adrenal-sympathetic syndrome" is the classical clinical picture in patients with pheochromocytoma. In typical cases the diagnosis is fairly simple, since there are paroxysms of hypertension associated usually with palpitation, severe headaches, extreme anxiety, severe sweating, nausea and vomiting, lacrimation and dilatation of the pupils. During such attacks there may be glycosuria, hyperglycemia, exophthalmos, swelling of the thyroid gland and the signs and symptoms of Raynaud's disease. These are all manifestations of the hypermetabolism produced by the outpouring of adrenalin into the blood. The blood pressure between attacks may or may not be elevated. It has been postulated that eventually all patients with

pheochromocytoma will develop a persistent hypertension in the interim between attacks of paroxysmal hypertension. In a small percentage of patients with pheochromocytoma, the blood pressure does not become elevated in paroxysms but remains persistently at high levels and accompanying evidences of increased metabolic activity are present. Patients afflicted with pheochromocytomas are very often already under treatment and observation for diabetes, hyperthyroidism or other metabolic diseases at the time the diagnosis is made. Many of these patients have tumors of other organs of the body. About 10% of patients with pheochromocytomas have von Recklinghausen's disease.

Approximately one-third of the case reports of chromaffinomata in the literature have notes on ocular examinations. Many of these reports are brief, and only about one-half of those which include ophthalmoscopic examinations make any mention at all of the condition of the retinal vessels. From the available literature I have been able to collect reports of 66 proved cases of hypertension associated with pheochromocytoma in which examinations of the ocular fundi had been included. To these I have added 4 previously unreported cases of paroxysmal hypertension caused by pheochromocytoma proved by surgery at the Mayo Clinic. These 70 cases are considered here and the retinal lesions analyzed.

For consideration of the retinal lesions present these cases may be divided into 3 groups: 1, those with paroxysmal attacks of hypertension but with normal blood pressure between attacks; 2, those with paroxysmal attacks of hypertension but with persistent elevation of blood pressure above 150 systolic or 90 diastolic between attacks; and 3, those with a persistently elevated blood pressure which gave no history of any form of paroxysmal episodes. In each of these

3 groups there occur cases which show: A, no pathological changes in the retinas; B, only hemorrhages in the retina; C, only vascular changes without exudates; and D, retinopathy or neuroretinopathy. These data are shown in Table 1.

died of congestive heart failure, and a pheochromocytoma of the adrenal was found at autopsy. Ophthalmoscopic examination revealed papilledema and many hemorrhages and exudates; no mention was made of the condition of the retinal arterioles. Goldner's pa-

TABLE 1.—RELATION OF HYPERTENSION TO OCULAR CHANGES.

	Paroxysmal Hypertension	Persistent Hypertension With Paroxysms	Persistent Hypertension Without Paroxysms	No. of cases	Total %
Normal Fundi	10	4	1	15	21.4
Hemorrhages only	4	2	0	6	8.6
Vascular changes without retinopathy	8	8	2	18	25.7
Retinopathy or Neuroretinopathy	2	23	6	31	44.3
Total	24 (34.3%)	37 (52.8%)	9 (12.9%)	70	100.0

Thus, it is seen that among 24 patients with normal blood pressure between attacks of paroxysmal hypertension, 10 (41.6%) had normal fundi, while only 5 of 46 patients (10.9%) with persistent elevation of blood pressure had no lesions in the retina. Four of the latter 5 had paroxysmal episodes and 1 had no such attacks. Among the 12 patients without persistent hypertension who had retinal lesions but no retinopathy, 4<sup>15,32,53,70a</sup> had only minimal to moderate sclerosis of the retinal arterioles, 2<sup>1,69</sup> had only arteriolar narrowing, and 1<sup>57b</sup> had grade 1 narrowing and grade 1 sclerosis. The notation on Baker and Rienhoff's case<sup>2</sup> stated only that there were arterial changes and a few hemorrhages in the retina. Four other authors<sup>38,56,62,64</sup> had merely noted hemorrhages in the retina without observing any changes in the retinal vessels. Thus, 6 of the 24 patients who did not have constant elevation of blood pressure are said to have had sclerosis of the retinal arterioles (25%). Two patients in whom the blood pressure was not elevated between the paroxysms had retinopathy. Bensis and Codonnis' patient<sup>6</sup> had a long history of kidney disease with renal stones. For 8 months he had paroxysmal attacks during which the blood pressure rose from 140/70 to 290/200. The patient

tient<sup>25</sup> showed about grade 1 narrowing and questionable sclerosis of the retinal arterioles, and there were many cotton wool patches and hemorrhages in the retina. There was complete return to normal after operation.

The second group of patients, those having persistent elevation of blood pressure in the interim between paroxysmal episodes, show a greatly increased incidence of retinopathy over the first group. Only 4 (10.5%) of these patients were reported as having normal ocular fundi. Hyman and Mencher's<sup>33c</sup> patient was reoperated by Calkins and Howard<sup>12a</sup> 4 years later because of persistent symptoms and another tumor was removed, with resultant complete cure. There had at no time been any change observable in the eye-grounds. Muntz, Ritchey and Gatch<sup>47</sup> reported a patient with paroxysmal hypertension and elevated interim blood pressure for 2 years. This patient had bilateral adrenal tumors and associated malignancy of the thyroid with metastases. This patient had only slight tortuosity of the arterioles with no sclerosis nor hemorrhages. During attacks, the authors noted scleral injection and exophthalmos. The other 2 patients<sup>28,61a</sup> with normal retinas were operated and cured.

Bartels and Wall<sup>7</sup> noted only many

small retinal hemorrhages in their diabetic patient who was 65 years old and had had paroxysmal hypertension for one year prior to his death. Washington and his collaborators<sup>68</sup> mention only a few recent hemorrhages at the optic disk margins in a patient who at autopsy was found to have severe necrotizing arteriolitis in many organs of the body. Of the 8 remaining patients in this group, 5 cases had about grade 1 narrowing and grade 1 sclerosis of the retinal arterioles. These were reported by Blacklock *et al.*<sup>3c</sup>, Kvale *et al.*<sup>36</sup>, Goldenberg, Snyder, and Aronow<sup>24c</sup> with description of fundi by Bruce<sup>11</sup>. The case reported by Beer, King and Prinzmetal<sup>6</sup> was also reported by Hyman and Mencher<sup>33a</sup> and by Calkins and Howard<sup>12b</sup>. The case of Engel, Mencher and Engel<sup>17</sup> was again reported by Hyman and Mencher<sup>33a</sup> and by Mencher<sup>45</sup>. Three cases<sup>44,57a,58</sup> had somewhat more marked vascular changes.

Of the 37 patients reported who had persistently elevated blood pressure between attacks of paroxysmal hypertension, 23 (62.2%) had retinopathy or neuroretinopathy. Several authors<sup>30,31a,31c,49,66</sup> mentioned only that albuminuric retinitis or hypertensive retinopathy was present, but they gave no detailed description of the retinal lesions. This was true also of Gortz's<sup>26</sup> patient reported by Espersen and Dahl-Iversen<sup>19</sup>. Rodin<sup>54</sup> published a very complete description of the ocular fundi in a patient with a pheochromocytoma successfully removed surgically. The case had been previously reported by Biskind, Meyer and Beadner<sup>8</sup>. Photographs of the retinas taken at intervals after surgery revealed the gradual disappearance of papilledema, hemorrhages, exudates, macular stars and narrowing of the retinal arterioles. The ocular fundi were reported as normal 3½ years after the operation. Five patients<sup>14,21,23,24c,27</sup> who had papilledema, hemorrhages and exudates

were said to have arterioles narrowed variously from grade 1 to "extremely spastic"<sup>21</sup>. All recovered and had a progressive improvement in the retinal picture postoperatively.

In this group of patients, it was much more common to have neuroretinopathy than it was merely to have cotton-wool patches and vascular changes. Papilledema was stated definitely to be absent in only 3 cases: those reported by Coller *et al.*<sup>13</sup>, Edward<sup>16</sup>, and the case published by Snyder and Vick<sup>60b</sup> with detailed ocular description by Bruce<sup>11</sup>. In addition to the 6 patients mentioned above in which papilledema was associated with spastic constriction of the arterioles, papilledema was noted in 9 patients<sup>20,22,18,40,48,51,55,60a,65</sup> associated with retinal arteriolosclerosis ranging from grade 1 to grade 3 and arteriolar narrowing ranging from grade 1 to grade 3. Most authors who took note of the arterioles remarked on the high degree of spasticity in the vessels, but only Green<sup>27</sup> and Volhard<sup>65</sup> commented on the presence of localized constrictions in the arterioles. Coller and his collaborators<sup>13</sup> mentioned the presence of endarteritis and periarteritis. Snyder and Vick<sup>60b</sup> and later Bruce<sup>11</sup> reported an 11 year old negro girl who had one paraganglioma at the bifurcation of the aorta and another in the right epigastric area. She was noted to have pronounced narrowing and tortuosity of the arterioles, nicking of the veins and beginning macular stars but no papilledema.

Among the 37 patients with paroxysmal hypertension but with persistence of elevated blood pressure between attacks, 16 (43.2%) were said to have retinal arteriolosclerosis.

Among the 9 patients with proved pheochromocytomas in whom the blood pressure was steadily elevated and no definite paroxysms occurred, 1 (11.1%) had normal ocular fundi, 2 (22.2%) had only retinal vascular lesions and 6 (66.7%) had retinopathy.

Linder and Tyler<sup>39</sup> reported a patient with chronic duodenal ulcers and with hypertension but without paroxysmal episodes who complained only of headaches and dizziness for 4 years, but was found to have a pheochromocytoma on autopsy. Her retinal vessels were reported to be normal. Thorn, Hindle and Sandmeyer<sup>63</sup> and Binger and Craig<sup>7</sup> each reported a patient with persistent hypertension cured by removal of a pheochromocytoma, neither patient having had paroxysmal hypertension. Both these patients had severe arteriolar narrowing. Thorn's patient had severe sclerosis, while Binger's patient had little or no sclerosis of the retinal arterioles, but did have grade 1 local spastic constrictions in the arterioles.

In 6 patients with persistent hypertension but without paroxysmal attacks, ophthalmoscopic examination revealed the presence of retinopathy. In 2, those of Brenner *et al.*<sup>10</sup> and Holst<sup>31b</sup>, the descriptions of the ocular fundi were rather brief. Brenner noted papilledema, narrowing of the arterioles, macular stars and numerous hemorrhages. Holst mentioned only poor vision and albuminuric retinitis in a 19 year old male with considerable fluctuations in blood pressure but no paroxysmal attacks. Kremer<sup>35</sup> mentions nephritic retinitis with arteriolosclerosis and bilateral optic atrophy in his patient. One of Snyder and Vick's<sup>60c</sup> patients, also reported by Goldenberg, Snyder and Aranow<sup>24a</sup> and by Bruce<sup>11</sup>, was a 12 year old girl who had no paroxysmal hypertension nor great fluctuations in blood pressure, which remained about 180-240 systolic and 120-170 diastolic. Her presenting complaint was excessive perspiration. Her eyes were at first normal, but she gradually developed papilledema, arterial spasm, venous compression, hemorrhages, exudates, and diminution of visual acuity coincident with the development of macular stars. Six months

after her 2 adrenal pheochromocytomas were removed, she had no papilledema, hemorrhages or exudates and the blood pressure was normal. Edward<sup>16</sup> noted hemorrhages, exudates, and irregular constrictions in the arterioles in a patient with pheochromocytoma who had had no symptoms prior to the sudden onset of hemiplegia. This patient died 7 days after this incident. His blood pressure remained constantly at 220-230/140 during this period.

A 21 year old girl was seen at the Mayo Clinic with a 3 year history of persistently elevated blood pressure, nervousness, severe sweating, marked intolerance to heat, and an elevated basal metabolic rate. She was discovered to have a pheochromocytoma of the right adrenal as well as a grade 2 carcinoma of the pancreas. Her eye-grounds showed papilledema, grade 2-3 narrowing, minimal sclerosis, and grade 2 focal constrictions in the arterioles. There were numerous cotton wool patches, hemorrhages and partial macular stars in both eyes. Postoperatively, there was a gradual regression of all retinal changes. At the present time, 1½ years following operation, her blood pressure is normal, she notes only mild heat intolerance, her basal metabolic rate is at the upper limits of normal and she has only about grade 1 narrowing of the retinal arterioles with complete 'disappearance of neuroretinopathy.

In this small group of 9 patients with constant hypertension, 5 (55.5%) were said to have retinal arteriolosclerosis.

Several authors observed the eye-grounds during the paroxysmal attacks of hypertension in their patients and reached varying conclusions. The patient reported by Kvale, Roth, *et al.*<sup>50</sup> was observed by Dr. H. P. Wagener during an attack. He could detect no change in the calibre or appearance of the retinal vessels. The same was

true in the patient reported by C. H. Mayo<sup>43</sup>. Hyman and Mencher<sup>33b</sup> and Evans<sup>20</sup> noted slightly increased narrowing and propulsive pulsation of the arterioles during an attack. Snyder and Vick's patient<sup>60a</sup> was examined during an attack in which the diastolic pressure was measured at 300 mm. of mercury. The pupils were then widely dilated, the papilledema increased, and the arterioles further constricted and there was increase also in hemorrhage, exudation and arteriovenous nicking. Lecuire *et al.*<sup>38</sup> reported that both the arteries and the veins in the retina dilated and the diastolic blood pressure in the central artery of the retina rose from 45 to 70 in their patient during an attack. Perera<sup>50</sup> noted that during attacks his patient showed very definite spasm of the arterioles, with considerable narrowing and irregularity.

Most authors report wide dilatation of the pupils and increased lacrimation during attacks of paroxysmal hypertension. Several<sup>47,62,69</sup> noted exophthalmos coincident with great increase in blood pressure. Philips<sup>51</sup> described a left-sided Horner's syndrome in the patient he reported who had a paraganglioma in the vicinity of the first left thoracic ganglion. He ascribed the Horner's syndrome to involvement of the efferent sympathetic fibers passing through the first thoracic ganglion from the spinal cord on their way to the cervical sympathetic chain.

Whether the elevation of blood pressure, originally paroxysmal in type, resulting from a pheochromocytoma, will become constant eventually in all cases is still a matter for conjecture. In this series there are 5 patients<sup>34,38,50,61b,62</sup> who had had paroxysms of hypertension for from 5 to 10 years. They each still had normal blood pressure between attacks when examined, and there was no retinopathy. And yet, if it is assumed that those patients who do have persistent hypertension have a

superimposed essential hypertension, the blood pressure should not return to normal after removal of the pheochromocytoma. Postoperative blood pressures are recorded in 25 of these patients. Among them the blood pressure remained slightly elevated in 6 (24%)<sup>7,8,13,14,25,28</sup>, in 5 of whom retinal arteriolosclerosis was present. The fact that retinal arteriolosclerosis was stated to be present in a fair percentage (38.6%) of these patients, would seem to indicate that elevation of blood pressure in itself, from whatever cause, can produce the ophthalmoscopic appearance, at least, of retinal arteriolosclerosis. It seems fairly well established that retinopathy and neuroretinopathy do not usually develop in patients with pheochromocytoma until the blood pressure becomes persistently elevated between attacks. However, it is evident from this series that the severe retinal changes can occur occasionally even with normal interim blood pressures<sup>6,25</sup>. It is of interest that 10 of the 70 cases occurred in children under the age of 16. In all of them, retinopathy was present.

As has been noted before by Bruce<sup>11</sup> and Wagener<sup>67</sup>, the retinopathy associated with the hypertension of pheochromocytoma is indistinguishable ophthalmoscopically from that of primary (essential) hypertension, although, as in the matter of arteriolosclerosis itself, the data is not too accurate or conclusive. It is of interest that among the 31 cases of retinopathy, 19 (61.4%) would seem to be of the acute hypertensive type without sclerosis of the arterioles.

A further matter of interest may be noted. In 5 cases<sup>8,24a,25,63,70d</sup>, there was reported a diminution in the degree of arteriolosclerosis of the retinal arterioles postoperatively. This would seem to indicate that in severe degrees of hypertension with severe narrowing of the retinal arterioles, there may be a heightened arteriolar light reflex which

simulates the higher degrees of sclerosis. This phenomenon would tend to be a misleading factor in assessing and interpreting vascular damage.

Since the ophthalmologist sees many of these patients primarily because of visual difficulties, he should bear in mind the possibility of the presence of this curable disease when confronted with hypertensive retinopathy, especially if the retinopathy is of the acute hypertensive type without associated

retinal arteriolosclerosis, and perhaps especially if it is seen in a child. The further point is brought out by a review of these cases that retinopathy with papilledema even in the presence of retinal arteriolosclerosis is not necessarily a fatal prognostic sign. The diagnosis of terminal malignant hypertension should not be considered as established until all possible causes of secondary hypertension have been ruled out.

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# PHYSIOLOGY

## PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 18, 1948

**Studies on the Action of a Synthetic Heparinoid\*.** JOSEPH SEIFTER, M.D., and ALBERT J. BEGANY, A.B. (Wyeth Institute of Applied Biochemistry, Phila.).

THE synthetic antithrombins available heretofore are too toxic for clinical use. However, Snyder and Alburn have recently prepared Hepinoid, a polysulfuric ester of polyanhydromannuronic acid, which does not appear to have this drawback. The pharmacology and toxicology of Hepinoid have been investigated in animals and humans and were found closely to resemble those of heparin. In the study briefly reported here, attention has been centered on elucidating the causes for the relatively rapid dissipation *in vivo* of a single therapeutic dose of heparin or Hepinoid.

The toxicity of Hepinoid was found to be no greater than that of heparin, and about 1/10 to 1/20 that of other heparinoids. This can be seen from the following list of LD<sub>50</sub> values determined as mg./kg. of mouse by intravenous injection: heparin, 1500-2000; Hepinoid, 189S; cellulose sulfuric ester, 100; oxycellulose sulfuric ester, 200.

The anticoagulant potency of therapeutic doses of Hepinoid in humans is 1/7 that of heparin. In all species tested, both the intensity and the duration of action are proportional to the dose administered. However, when relatively large doses are administered, such as 1/10 the LD<sub>50</sub>, the potency of both anticoagulants are practically identical and the duration of action is prolonged for 10 to 11 hours.

The relatively brief duration of action of heparin has been variously attributed to urinary excretion, phagocytosis by the reticulo-endothelial cells, destruction by the enzyme heparinase, and inactivation by thromboplastic substances in the tissues. Experiments were made, therefore, to determine whether Hepinoid was inactivated by any of these mechanisms and also to determine how valid these are for heparin.

Following intravenous injections of therapeutic doses of heparin or Hepinoid it was never possible to recover more than 30% in the urine. It appeared, therefore, that excretion of these substances in the urine is not the important factor in the dissipation of their action. This was conclusively confirmed when bilateral nephrectomy failed to prolong the anticoagulant effects of a therapeutic dose of either substance.

Nor was the duration of anticoagulation significantly affected by any of the following procedures: splenectomy; complete hepatectomy; combined nephrectomy, splenectomy, and hepatectomy; injections into the bone marrow of the tibia; ligation of the carotid and vertebral arteries; blockade of the reticulo-endothelial system with India ink—to the point where frequently an endogenous anticoagulant is released; stimulation of the reticulo-endothelial system by histamine, and depression of it by antihistaminic drugs. All of these negative results exclude the following as being responsible for the relatively brief effect of a therapeutic dose of heparin or Hepinoid: urinary excretion,

\* The term Heparinoid is introduced to include all the synthetic antithrombins, in order to distinguish them from the naturally occurring Heparin.

as already mentioned; enzymatic destruction in the liver; inactivation by thromboplastic substances in certain tissues; and phagocytosis by cells of the reticulo-endothelial system. Phagocytosis was seen in intact animals, but was most active after the anticoagulant effect had worn off.

Heparin and Hepinoid appear, therefore, to be inactivated in the peripheral blood stream, and indeed the results of current *in vitro* experiments tend in this direction. The inactivating agent appears to be an antithrombin inhibitor.

**Glycolysis in Homogenates and Extracts of Malignant Tumor.** OTTO MEYERHOF, M. D., and JEAN R. WILSON, M. S. (Dept. of Physiological Chemistry, Univ. of Penna.).

IN homogenates and centrifugal extracts of malignant tumor a steady glycolysis of free sugar of a rate 2 to 3 times that of tissue slices is obtained if the activities of the hexokinase and the ATPase are brought into step. This is made possible either by addition of purified hexokinase from yeast or without any foreign enzyme if the tumor ATPase is specifically inhibited.

ATPase of tumor is weakened by several days' freezing but with still greater regularity by narcotic or specific inhibition. Most effective are very high members of narcotic series; octyl-, decyl-, and dodecylalcohol and toluene are suited best. A similar effect is obtained with about M/100 of Na azide. Most work was done with octyl alcohol. The strong inhibition of the ATPase of tumor by higher members of the narcotic series is remarkable because the ATPase of normal tissues is only slightly affected, sometimes in the direction of inhibition, sometimes in the direction of activation.

With octylalcohol  $Q_{La}$  values of homogenates of 50-60 are easily obtained and somewhat smaller (40 - 45) for extracts. The differences in the turnover rates for various sugars, especially for glucose and fructose closely

resemble those of the living tumor tissue in the absence of inhibitors.

**Further Studies of the Effect of Hypertonic Glucose on the Circulation.** JAMES P. WALSH, M. D. (Dept. of Therapeutic Research and of Medicine, Univ. of Penna.).

THE initial studies (unreported) by Dr. Marcel Segers and the author had demonstrated that after the rapid intravenous injection of 50 cc. of 50% glucose in 14 subjects with cardiac disease, there was a prolonged increase in cardiac output as measured by the ballistocardiograph. In contrast, in 9 subjects with normal hearts, although the cardiac output increased initially, it returned to the basal level in 6 to 8 minutes. There was little or no change in blood pressure or cardiac rate after the glucose injection in either normal or cardiac patients.

Further studies after similar injections of glucose included the measurement of peripheral venous pressure by a saline manometer in 2 normal subjects and 4 with heart disease; and of plasma volume by the dye T-1824 in 4 normal subjects and 10 with heart disease. These determinations and estimates of cardiac output by the ballistocardiograph were made at intervals of 5 to 15 minutes for 30 to 45 minutes after the glucose injection.

There was a small initial increase in peripheral venous pressure after glucose injection with a prompt return to the basal level. In 45 paired estimations of cardiac output and plasma volume, there was a statistically significant correlation between the changes occurring in each after the injection (correlation coefficient 0.41). However, this correlation was not a close one and change in plasma volume was by no means always followed by a concomitant change in cardiac output.

Since the change in blood volume affects venous pressure so little, it probably does not cause the prolonged increase in cardiac output; so there

may well be a specific stimulating effect of glucose on the failing myocardium as has been observed in the animal heart-lung preparation.

**Further Studies on Intraarterial Temperature.** LEON EISENBERG, M. D., and H. C. BAZETT, M. D. (Dept. Physiol., Univ. of Penna.)

PREVIOUS reports have given evidence of considerable exchange of heat between cool blood returning in venae comites from the periphery of limbs and warm blood flowing out of adjacent arteries. Thereby venous blood is rewarmed at the expense of arterial cooling, even to temperatures below 22° in the radial artery. The existence of such exchanges may be demonstrated readily in animals by perfusing a femoral vein with cooled saline. A steep thermal gradient may thus be set up within a short length of femoral artery, which varies with the rates of flow in both artery and vein.

General reflexly-induced vascular re-

sponses to warmth are discussed in the literature without regard to the complexities introduced by vasodilation and these thermal exchanges, which can account for the long delay in observed effects. Exposure of the hands to hot water may induce a rise in temperature in the dorsalis pedis within one minute but this can be counteracted by a simultaneous fall in temperature in central vessels. Increased blood flow raises thermal conductance, redistributing heat and warming the colder peripheral areas at the expense of those that are warmer and more central. Vasodilation causes not only greater inflow of blood but also more rapid return of cooled venous blood. Even in an artery as peripheral as the radial these effects can for some time compete with one another, delaying a rise of temperature or even producing an initial fall as the result of vasodilation.

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# BOOK REVIEWS AND NOTICES

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**HISTORY OF MEDICINE.** By CECILIA C. METTLER, PH.D., late Asst. Prof. of Medical History, Univ. of Georgia. Pp. 1215; 16 ills. Phila.: Blakiston, 1947. Price, \$8.50

FORTUNATELY the manuscript of this latest addition to systematic works on medical history, which we are told was under preparation for somewhat over 9 years, was completed shortly before the untimely death of its talented authoress. For it is a valuable contribution, both in the utility of its novel approach, in the general accuracy of its considerable factual content, and in the very liberal use of quotations from the writings of the great figures of the past. These, easily picked out in small type, range from 5 or 6 lines to 2 or more pages in length and probably constitute an eighth or more of the text. Thus in the 40 pages devoted to Pathology and Bacteriology, there are over 30 such excerpts.

As a zealous but honest professional teacher of medical history, Dr. Mettler appreciated the comparative failure of its teaching to medical students in this country. This and her belief in the value of medical history in aiding the study of medicine, as opposed to its "dubious cultural value", has largely determined the general form of the book. To aid in teaching the subject "on a correlative basis", the Contents are arranged under 15 main topics, corresponding in general to those of the average medical curriculum. Each of these is subdivided, mostly chronologically but also at times geographically or by special subjects, such as *Morbus Gallicus*. The Twentieth Century, already among the greatest in medical achievement, has not been included. Therefore, if the history of such classical discoveries as insulin, liver extract, the virus diseases and the rest that crowd in increasing measure each decade of the century is to be correlated with the curriculum, it must be without the help of this book.

The book will, to be sure, be useful in giving the medical student "an introduction to the principles underlying the development of the fields" of his curriculum, and in providing some familiarity with "the climate of opinion" surrounding a given advance or period. But when it is also aimed "to meet

the particular needs of the specialist who is interested in a single field", this simply can't be done properly, any more than it can in any other one volume history of such a vast subject. To be sure, the seeker is aided by copious reference notations—every column contains one or more references to individual authors or incidents—and in addition at the end of every chapter are found several pages of selected readings covering various subdivisions of the chapter.

How will this attractive book be of use and earn the success that it deserves? As supplementary to an inspiring teacher, the student being given adequate time, it should correlate the subject more easily than other works of its kind. There will be some medical history readers who will get from it the entertainment and scholarly or recondite background sought by the author, and this frequently reinforced by the original writer's own words. A good index, too, increases its value as a book of reference. The unusual arrangement of chapters of course will tend to hinder progressive reading, but who reads such books as simple narratives anyhow?

The book, then, may be said to occupy a middle position between the conventional Histories and such a series as *Clio Medica* (taking the series as a whole), with a dash on the side of such anthologies as *Classical Descriptions of Disease*. It will be a welcome addition to the medical history shelf. E. K.

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**RESEARCHES ON NORMAL AND DEFECTIVE COLOUR VISION.** By W. D. WRIGHT, A.R.C.S., D.Sc. Technical Optics Section, Imperial College of Science and Technology, London. Pp. 383; 233 ills. St. Louis: C. V. Mosby, 1947. Price, \$10.00.

THE first 2 chapters in this book serve as an introduction to the eye as a sense organ. In this section, the physiology of the retina is briefly reviewed in the light of recent knowledge. The rest of the book is largely composed of data on color vision obtained by the author's own researches. He is well known in this field and those who are interested in color vision will find much data of value. The book is not recommended for those who have not had laboratory experience in this field.

F. A.

**DYNAMIC ASPECTS OF BIOCHEMISTRY.** By ERNEST BALDWIN, B.A., Ph.D., University Lecturer in Biochemistry, formerly Fellow of St. John's College, Cambridge. Pp. 457; 33 figs. New York: Macmillan, 1947. Price, \$4.00.

THE vital aspects of 2 leading fields in biochemistry—enzymes and metabolism—are rather thoroughly considered in the light of past and new developments. The book is written from an investigator's viewpoint and is not a mere collection of facts. Historical development of different phases are included, which makes for easier understanding. Experiments are often described in considerable detail, and experimental methods are criticized in unbiased fashion. The text runs the gamut of enzyme systems and includes the new concepts of high energy exchange in ATP metabolism. Fat, protein, and carbohydrate metabolism is thoroughly discussed and illustrated with ample formulae. There is an interesting chapter on comparative aspects of nitrogen excretion. Where gaps in knowledge exist, speculation is often resorted to, but the author usually indicates clearly the speculative phases. I. Z.

**MEDICINE. (Volume I) THE PATIENT AND HIS DISEASE.** By A. E. CLARK-KENNEDY, M.D., F.R.C.P., Fellow of Corpus Christi College, Cambridge; Physician to the London Hospital and Dean of the Medical School. Pp. 383. Baltimore: Williams & Wilkins, 1947. Price, \$6.00.

THIS book is another brave attempt to achieve the impossible; "it is intended to inculcate an attitude of mind. It is written to present facts which could be deduced from principles being committed to memory unnecessarily". This highly desirable goal is unfortunately not reached by this volume.

Chapter I in 38 pages discusses "Energy and matter—Life—Organic evolution—Heredity—Development—Constitution—Consciousness and mind." At this rate it is easy to see how much can be crowded into the remaining 341 pages. Actually, an enormous number of flat statements are made and there is a disappointing lack of the integration which the author hoped to present.

In the hurried attempt to cover everything, it is inevitable that dogmatic unqualified statements are made. Many of these are misleading, to a student. One, on page 153, is inexcusable "A rectal examination, easy under hospital discipline and routine, more difficult under other circumstances, is necessary in adult pa-

tients with diarrhoea, rectal bleeding, or prostatic symptoms and in every obscure or difficult case." Shades of Sir William Osler! A rectal examination is an integral part of the routine examination of every patient. O. P.

**THE BIOLOGY OF MELANOMAS.** Edited by ROY WALDO MINER, MYRON GORDON, and LOTHAR SALIN. Vol. Pp. 478; 107 plates. New York: The New York Academy of Sciences, 1948. Price, \$5.00. (To members, \$4.00.)

The experiments and interpretations collected in this volume do much to clarify the poorly understood subjects of pigment biology and pigmented tumors. Each chapter is written by a different group of authors, and the approaches to the subject vary widely. The aspects considered range from genetics of pigmentation to the chemistry of melanin. Many papers deal with pigmentation of the lower animals, and in relatively few chapters are specifically human aspects considered. Of particular interest are the chapters written by Masson, by Becker, and by Du Shane on pigment cells in man and in the vertebrates. All papers on morphologic subjects are followed by excellent black and white illustrative photographs. A. R.

**PUBLIC HEALTH ADMINISTRATION IN THE UNITED STATES.** By WILSON G. SMILLIE, M.D., Prof. of Public Health and Preventive Medicine, Cornell Univ. Medical College, 3rd ed. Pp. 637; 43 ills. New York: Macmillan, 1947. Price, \$6.50.

THIS edition, like its predecessors, is aimed to elicit the interest of the practicing physician in disease prevention and control. The text is so clear and each subject is discussed so completely and satisfactorily, that the author's aim has obviously been achieved. The volume is a superior textbook for students and an indispensable reference work and guide for health officers.

Here we find, in their proper places, all the great developments from research, speeded up so productively during World War II and since, which are transforming our concepts of disease control in many fields.

The final chapter discusses with great wisdom the development and the details of "The National Health Program." This reviewer is not acquainted with a more clarifying exposition of this matter which has been the subject of so much controversy. A. H.

## NEW BOOKS

*Modern Trends in Dermatology.* Edited by R. M. B. MacKENNA, M.A., M.D. (Camb.), F.R.C.P. (Lond.), Lecturer in Dermatology, St. Bartholomew's Hospital, London. Pp. 432; 32 ills. New York: Paul B. Hoeber, 1948. Price, \$8.50.

*Physical Treatment of Injuries of the Brain and Allied Nervous Disorders.* By K. M. HERN, M.C.S.P., Diploma of Liverpool Physical Training College. Pp. 96; 34 ills. Balt.: Williams & Wilkins, 1947. Price, \$4.00.

*Glomerular Nephritis.* By THOMAS ADDIS, M.D., F.R.C.P. (Edin.). Pp. 338; 56 figs. New York: Macmillan, 1948. Price, \$8.00.

*Biology of Disease.* By ELI MOSCHOWITZ, M.D., Mt. Sinai Hospital Monograph No. 1. Pp. 221. New York: Grune & Stratton, 1948. Price, \$4.50.

*Pediatrics for Nurses.* By ARTHUR G. WATKINS, M.D., F.R.C.P., Lecturer Welsh National School of Medicine. Pp. 192; 22 ills. Balt.: Williams & Wilkins, 1948. Price, \$3.50.

*Feeding Problems in Man as Related to Environment. An Analysis of U. S. and Canadian Army Ration Trials and Surveys, 1941-1946.* By ROBERT E. JOHNSON, M.D., and ROBERT M. KARK, M.R.C.P. (Lond.). Pp. 94; 13 figs. Chicago: Quartermaster Food and Container Inst. for the Armed Forces, 1948.

*The 1947 Year Book of Pathology and Clinical Pathology.* Edited by HOWARD T. KARNER, Prof. of Pathology, Western Reserve Univ., HERBERT Z. LUND, M.D., and ARTHUR HAWLEY SANFORD, M.D., Prof. of Clinical Pathology, Univ. of Minnesota. Pp. 558; 102 ills. Chicago: Year Book Publishers, 1948. Price, \$3.75.

*Voluntary Medical Care Insurance in the United States.* By FRANZ GOLDMANN, M.D. Pp. 228. New York: Columbia Univ. Press, 1948. Price, \$3.00.

"A COMPANION volume to *Public Medical Care* by the same author . . . It traces the progress of major types of programs from the mid-19th century to the present . . . summarizes the limitations and possibilities of the entire principle of voluntary medical care insurance."

*Chronic Ill-Health.* By ROSA FORD, M.B. (Lond.), D.O. (Oxon.), Late Ophthalmic Surgeon, South London Hospital for Women. Pp. 104; 13 ills. London: Henry Kimpton, 1948. Price, \$3.00.

*What Is Psychoanalysis?* By ERNEST JONES, M.D. Pp. 126. New York: International Universities Press, 1948. Price, \$2.00.

*Akute Aussere Prozesse die Physiologie, der Chirurgischen und Konservativen Therapie.* von DR. JOSEF RIESE, Privatdozent für Chirurgie, Universität Wien. Pp. 326. Wien: Wilhelm Maudrich, 1948. No price given.

*Klinisch-Praktische Bewertung des Elektrokardiogramm-Befundes.* von DR. OSKAR v. ZIMMERMANN-MEINZINGEN. Pp. 227; 136 ills. Wien: Wilhelm Maudrich, 1948. No price given.

*Projective Methods.* By LAWRENCE K. FRANK, Director, Zachry Institute of Human Development, New York. Pp. 86. Springfield, Ill.: Charles C. Thomas, 1948. Price, \$2.75.

THE author describes the tendency in all science nowadays to study process rather than structure, and goes on to show that projective tests are trying to give initial understandings of both the general process of personality development and the special processes of the individual person, with no interest in statistically established norms. There is an excellent bibliography of 18 pages.

The reader will find this book a short evaluation of projective methods against the large background of psychology and science. E. B.

*The Clinical Picture of Thyrotoxicosis.* By PETER McEWAN, M.A., M.B., Ch.B., F.R.C.S. (Edin.). Pp. 127; 4 ills. Edinburgh and London: Oliver and Boyd, 1948. Price, 15/- net.

THIS small book presents the clinical symptoms of thyrotoxicosis in a simple, readable fashion. There is little attempt made to explain the pathologic physiology underlying them and none to discuss organic changes which present few symptoms, as for example, lesions in the liver. The mortality figures and geographic distribution of the disease that are given are for England.

The reviewer does not recommend the book for the specialist and doubts its usefulness to the average general practitioner, although certain symptoms are discussed which are not commonly thought of as important in thyroid disease. I. R.

*Pathology of Tumours.* By R. A. WILLIS, D.Sc., M.D., F.R.C.P., SM WILLIAM H. COLLINS, Prof. of Human and Comparative Pathology, Royal College of Surgeons, London. Pp. 1050; 500 ills. St. Louis: C. V. Mosby, 1948. Price, \$20.00.

*Rheumatism and Soft Tissue Injuries.* By JAMES CYRIAX, M.D., B.Ch. (Cantab.), Physician-in-Charge, Physiotherapy Dept., St. Thomas's Hospital, London. Pp. 410; 107 ills. New York: Paul B. Hoeber, 1947. Price, \$9.50.

*Fundamentals of Human Reproduction.* By EDITH L. POTTER, M.D., Assoc. Prof. of Pathology, Department of Obstetrics and Gynecology, Univ. of Chicago. Pp. 231; 92 figs. New York: McGraw-Hill, 1948. Price, \$3.50.

Written for nurses, its clear simplification may also be useful to medical students.

of the important developments of the past few years.

*Progress in Clinical Medicine*. Edited by RAYMOND DATEY, M.A., M.D., Camb., M.B.C.P., and HENRY G. MILLER, M.D., Durh., M.R.C.P., D.P.M. Pp. 356, 22 figs., 15 plates. New York: Grune & Stratton, 1948. Price, \$6.00.

Twelve British physicians present some of the important developments of the past few years.

*Topics in Physical Chemistry*. By WILLIAM MANFIELD CLARK, Ph.D., Sc.D., Delamar Hopkins Univ. Pp. 738. Balt.: Williams & Wilkins, 1948. Price, \$10.00.

As the title implies, this book is not a

text on physical chemistry, nor is it to be

taken as a complete reference book. It is

rather a series of stimulating dissertations

on various aspects of physical chemistry—

such as gas laws, thermodynamics, dif-

fusion, semipermeable membranes, mass-

action laws, oxidation-reduction systems and

a host of other related and unrelated topics.

Numerous techniques are described and

special attention is given to possible sources

of error. In some sections there is a lack of

continuity in the text. Much useful informa-

tion, as well as thought-provoking treat-

ment of many subjects, makes it valuable

to scientists in most fields.

*Man - Weather - Sun*. By WILLIAM F. PETER-

SEN, M.D. Pp. 462, 294 figs. Springfield,

Ill.: Charles C. Thomas, 1948. Price, \$10.00.

This is a further presentation by Dr.

Petersen of his studies and speculations on

the interrelation of the human organism and

its inorganic environment, leading to the

concept of "man as a cosmic resonator."

One of its more interesting features is a

detailed six weeks' day-by-day study of

adult triplets, extending over 100 pages.

*The Back and Its Disorders*. By PHILIP LEWIN,

M.D., F.A.C.S., Prof. of Bone and Joint Sur-

gery, Northwestern Univ. Medical School.

Pp. 157, 15 illus. New York: McGraw-Hill,

1948. Price, \$2.50.

This book is intended as a guide for the

layman, briefly describing conditions and

mechanisms causing backache. It is not a

diagnostic guide. The author has attempted

to give laymen a description of the anatomy

and physiology of the back. The difficulties

of diagnosis and treatment are stressed.

P. C.

## NEW EDITIONS

*Endotracheal Anesthesia*. By NOEL A. GIL-  
LESPIE, M.A. (Oxon.), M.D. (Wis.), Assoc.  
Prof. of Anaesthesia, Univ. of Wisconsin.

2nd ed. Pp. 237, 56 figs.; 1 color plate.  
Madison: University of Wisconsin Press,  
1948. Price, \$4.00.

This edition represents the revision and

enlargement of a work which, even

without such improvements, was outstand-

ing. Fifty pages have been added. The ad-

vances in endotracheal anesthesia during

the past 5 years have been summarized.

The only criticism the reviewer has is of

the quality of paper and the print. The first

edition was preferable from these stand-

points.

*Diseases of the Nose, Throat and Ear*. By

I. SAXSON HALL, M.B., Ch.B., Surgeon to

the Royal Infirmary, Edinburgh. 4th ed.

Pp. 463, 34 illus., 8 color plates. Balt.: Wil-

liams & Wilkins, 1948. Price, \$4.50.

This well-illustrated concise and elementary

text-book has been brought up to date by includ-

ing such topics as the fenestration operation and

penicillin. Designed for the busy practitioner and

the student, it serves as a brief introduction to

otolaryngology but is too superficial to serve as

a reference work.

H. S.

*Stethoscopic Heart Records*. By GEORGE D.

GECKLER, M.D., Assoc. Prof. of Medicine,

Hahnemann Medical College. Revised edi-

tion. New York: Columbia Records, Inc.

Set M-735. No price given.

Four 12 inch records, with a printed statement

on the inside of the cover about their purpose

and use.

*Bergey's Manual of Determinative Bacteriolo-*

*gy*. Edited by ROBERT S. BURED, New York

State Experiment Station, Cornell Univ.,

E.C.D. MURRAY, McGill Univ., and A.

PARKER HITCHENS, Univ. of Pennsylvania.

6th ed. Pp. 1529. Balt.: Williams & Wil-

kins, 1948. Price, \$15.00.

The present edition of Bergey's well-known

manual is a complete revision of the 1939 volume.

It has been reset in double column format and

the amount of material included has been greatly

increased. Almost 300 additional species are de-

scribed. The viruses and rickettsiae are included

for the first time. An extensive Source and Habitat

index is also new.

This authoritative reference work will continue to

be indispensable in all laboratories of bacteriology.

C. B.

*An Introduction to Physical Methods of Treat-*

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## ORIGINAL ARTICLES

### EFFECT OF ORAL CARONAMIDE ON PLASMA PENICILLIN LEVELS FOLLOWING LARGE INTRAMUSCULAR DOSES OF PENICILLIN\*

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Because of the rapid renal clearance of penicillin, the maintenance of levels adequate to control infections caused by organisms that are comparatively resistant to penicillin requires administration of the antibiotic in very large amounts either by constant intravenous infusion, or by frequent intramuscular injections.<sup>1,16,17</sup> Both diodrast<sup>15</sup> and para-aminohippuric acid<sup>3,10-12</sup> will block the tubular excretion of penicillin and consequently enhance the plasma levels that are obtainable from any given dose. Clinical use of these agents as adjuncts to penicillin therapy, however, has been limited because they are effective only when given intravenously in large amounts. Several groups of workers have reported that plasma penicillin levels can also be

enhanced by the oral administration of benzoic acid or sodium benzoate.<sup>6,7,20,21</sup> Others, however, have found benzoic acid to have little effect on penicillin levels.<sup>4</sup>

Recently Beyer<sup>2</sup> reported that the excretion of penicillin could be reversibly inhibited by 4'-carboxyphenylmethanesulfonanilide (caronamide). Several reports have appeared showing that caronamide given by mouth significantly enhances penicillin blood levels in man.<sup>4,5,18,21</sup> In view of the need for very high levels in the occasional patient, it seemed of interest to study the effect of caronamide on the penicillin plasma levels following the administration of single doses of 1 million units. A few observations were also made on the effect of sodium benzoate:

\* Aided by a grant from the United States Public Health Service.

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**Materials and Methods.** The subjects were all convalescent male hospital patients. Since persons over 60 years of age excrete penicillin more slowly and also require less caronamide to enhance the blood levels than do younger people,<sup>18</sup> subjects in both of these age groups were included in this study. Also since renal disease<sup>16</sup> and congestive heart failure<sup>13</sup> may delay penicillin excretion, no patient was selected who was in heart failure or in whom there was obvious impairment of renal function. Otherwise patients were chosen without regard to their disease. They were given the regular hospital diet; fluid and salt intake was not controlled.

Commercially available penicillin G\* was used exclusively. Citrated bloods for penicillin plasma levels were obtained in each subject at suitable intervals following the intramuscular injection of 1 million units (dissolved in 3 cc. of physiological saline) before, during and after caronamide was given. The concentrations of penicillin were assayed by the serial dilution method of Rammelkamp,<sup>14</sup> modified only by the use of 0.5 ml. of the plasma dilutions. The caronamide was given by mouth in the form of tablets ground and suspended in flavored milk; the older people were given 2 gm. every 4 hours while the younger ones were given 4 gm. every 4 hours. The caronamide doses were started 12 hours before the penicillin injection in order to permit the drug to reach an equilibrium in the body fluids and were then continued for 24 hours after the penicillin was given. At least 24 hours was allowed to elapse following the last dose of caronamide before the postcaronamide control curve of penicillin blood levels was determined.

Two patients under 60 and two patients over 60 years old in whom the penicillin levels had been significantly enhanced by caronamide were chosen for a study of the effect of sodium benzoate. This was given as a 10% chilled aqueous solution. These patients were given 2 gm. of sodium benzoate every 2 hours beginning 3 hours before the million unit dose of

penicillin and continuing for 24 hours. A few days later, similar observations were made in the same subjects with the sodium benzoate given in doses of 4.5 gm. every 2 hours for 12 hours. This was preceded by 4 doses of 6 gm., each given 4 hours apart, the last one coinciding with the penicillin dose.

**Results.** *Effect of Caronamide in Patients Over 60 Years of Age.* The plasma penicillin levels resulting from the intramuscular injection of 1 million units in 7 patients over 60 years of age before, during and after oral therapy with 2 grams of caronamide every 4 hours are shown in Table 1. The caronamide therapy had little or no effect on plasma penicillin levels in Patient 4, but its effect on the penicillin levels in the remaining 6 patients was striking. The peak penicillin levels obtained during caronamide were on the average twice as high as those obtained without caronamide. Six hours after the penicillin was administered the levels with caronamide were about 10 times as high as those without caronamide and at 12 hours the difference was more than 20-fold. At 18 hours and 24 hours the penicillin levels with caronamide averaged about 0.56 and 0.16 units, respectively, whereas at these times little or no penicillin could be detected in the control plasmas. In Patient 6 the levels resulting from the dose given 24 hours after the caronamide was discontinued were almost as high as those obtained during the caronamide administration. That his kidneys were not permanently damaged is shown by the essentially normal penicillin response curve obtained 2 days later when the effect of sodium benzoate was studied the first time. Presumably this patient retained sufficient caronamide to affect penicillin excretion significantly for at least 36 hours.

\* Generously supplied by Commercial Solvents Corporation.

TABLE 1. PLASMA PENICILLIN LEVELS IN PATIENTS OVER 60 YEARS OLD AFTER SINGLE INTRAMUSCULAR INJECTIONS OF 1 MILLION UNITS OF PENICILLIN WITH OR WITHOUT CARONAMIDE OR SODIUM BENZOATE BY MOUTH

Patient	Age	Caronamide Grams Every 4 Hr.	Sodium Benzoate Grams Every 2 Hr.	Hours After Penicillin Dose					
				0	1	6	12	18	24
1	70	0		0	16.0+	0.5	0.06	0	0
		2		0	16.0	4.0	0.5	0.25	0.06
		0		0	4.0	0.5	0.06	0	0
2	72	0		0	8.0	0.5	0.06	0	0
		2		0	16.0	8.0	4.0	1.0	0.25
		0		0	4.0	0.5	0.12	0.02	0
3	67	0		0	16.0	1.0	0.06	0	0
		2		0	16.0	4.0	0.5	0.12	0.03
		0		0	8.0	0.5	0.02	0	0
4	80	0		0	8.0	0.25	0.03	0.02	0
		2		0	16.0	0.25	0.06	0.03	0
		0		0	8.0	0.25	0.02	0.02	0
5	82	0		0	8.0	2.0	0.12	0.02	0
		2		0	32.0	16.0	8.0	2.0	0.25
		0		0	16.0	2.0	0.5	0.02	0.02
6	73	0		0	8.0	1.0	0.06	—	—
		2		0	32.0	16.0	4.0	0.5	0.5
		0		0	8.0	16.0	4.0	—	0.12
			2	0	16.0	2.0	0.12	0.03	0.02
			4.5	0	16.0	8.0	2.0	—	—
7	73	0		0	8.0	0.25	0.02	—	—
		2		0	16.0	4.0	0.25	0.03	0.02
		0		0	2.0	0.12	0	—	0
			2	0	16.0	0.25	0.02	0	0
			4.5	0	16.0	0.25	0.02	—	—
Average		0		0	10.3	0.73	0.06	0.01	0
		2		0	20.6	7.46	2.5	0.56	0.16
		0		0	7.1*	0.65*	0.12*	0.01	0

+ Units per ml. of citrated plasma; —, not done.

\* Excluding Patient 6.

*Effect of Caronamide in Patients Under 60 Years of Age.* Plasma penicillin levels obtained in 10 patients under 60 years of age before, during and after oral administration of 4 gm. of caronamide every 4 hours are listed in Table 2. While the degree of enhancement varied widely among these patients, the plasma penicillin levels without exception were definitely higher during caronamide therapy than in the control periods. As was the case in the older people, caronamide had only a slight effect on the peak levels

obtained in most cases, but it markedly altered the slope of the plasma level curve. During caronamide therapy, the peak penicillin levels were increased about 3-fold on the average, while after 4 hours the average difference was about 15-fold. Without caronamide little or no penicillin remained in the plasma 8 and 12 hours after the penicillin dose, while with caronamide an average of about 0.4 units was still present at 8 hours, and 0.1 unit at 12 hours. In 5 of the 10 patients penicillin could still be de-

TABLE 2. PLASMA PENICILLIN LEVELS IN PATIENTS UNDER 60 YEARS OLD AFTER SINGLE INTRAMUSCULAR INJECTIONS OF 1 MILLION UNITS OF PENICILLIN WITH OR WITHOUT CARONAMIDE OR SODIUM BENZOATE BY MOUTH

Patient	Age	Caronamide Grams Every 4 Hr.	Sodium Benzoate Grams Every 2 Hr.	Hours After Penicillin Dose						
				0	1	4	8	12	18	24
8	14	0		0	2.0+	0.12	0	—	—	—
		4		0	4.0	0.25	0.02	0	0	0
		0		0	2.0	0.12	0	0	—	—
9	26	0		0	4.0	0.25	0.02	0	—	—
		4		0	8.0	2.0	1.0	0.25	0.06	0
		0		0	4.0	0.06	0	0	0	—
10	46	0		0	2.0	0.06	0	0	—	—
		4		0	2.0	0.25	0.02	0	0	0
11	52	0		0	4.0	0.25	0.03	0.02	—	—
		4		0	4.0	2.0	0.5	0.25	0.02	0
		0		0	4.0	0.12	0.03	0	—	—
12	38	0		0	2.0	0.12	0	0	—	—
		4		0	4.0	0.5	0.25	0.02	0	0
		0		0	4.0	0.25	0	0	—	—
13	38	0		0	4.0	0.12	0.02	0.02	—	—
		4		0	16.0	4.0	0.5	0.06	0.02	0
		0		0	2.0	0.06	0.02	0	—	—
14	30	0		0	2.0	0.06	0	0	—	—
		4		0	4.0	2.0	0.06	0	0	0
		0		0	2.0	0.02	0	0	—	—
15	18	0		0	8.0	0.12	0.03	0.02	—	—
		4		0	16.0	2.0	0.25	0.06	0	—
		0		0	4.0	0.03	0	0	—	—
16	42	0		0	4.0	0.25	0.02	0	—	—
		4		0	16.0	2.0	0.25	0.06	0.02	0
		0		0	2.0	0.25	0	0	—	—
			2	0	8.0	0.25	0	0	0	0
			4.5	0	8.0	0.25	0.02	0	0	0
17	38	0		0	8.0	0.25	0.02	0	—	—
		4		0	32.0	8.0	1.0	0.25	0.03	0
		0		0	2.0	0.25	0	0	—	—
			2	0	8.0	0.25	0.02	0	0	0
			4.5	0	8.0	0.75	0.03	0	—	—
Average		0		0	4.0	0.16	0.01	0.01	0	0
		4		0	10.6	2.30	0.39	0.10	0.02	0
		0		0	2.9	0.16	0.01	0	0	0

: Units per ml. of citrated plasma; —, not done.

tected in the plasma as late as 18 hours after its administration.

*Comparison of Effects of Caronamide and Sodium Benzoate.* The plasma penicillin levels during the administration of sodium benzoate are shown for patients 6 and 7 in Table 1

and for patients 16 and 17 in Table 2. Two grams of sodium benzoate given every 2 hours had little if any effect on the penicillin curves. The experiment was then repeated in the same individuals with doses of 4.5 gm. every 2 hours following 12 hours of priming

with 6 gm. every 4 hours. One of the older patients, Number 6, showed a moderate enhancement of penicillin levels when he was given the larger dosage of sodium benzoate. This effect, however, was much less marked than that produced by 2 gm. of caronamide every 4 hours in the same patient. The sodium benzoate did not significantly alter the penicillin levels in the other 3 patients.

*Untoward Effects of Caronamide.* Urinalyses and blood nonprotein nitrogen determinations were done before, during and after the caronamide administration. Slight reduction of Benedict's solution (blue-green reaction) was observed in occasional urines during caronamide administration. Crystalluria, albuminuria or formed elements were not found in the freshly voided

urines and the blood nonprotein levels all remained within normal limits. The only untoward effects encountered were nausea in 4 patients with vomiting in 2 of them.

*Comment.* The average penicillin levels obtained following 1 million units of penicillin with and without caronamide are plotted in Figure 1. Data obtained in a previous study<sup>18</sup> on the effect of caronamide with intramuscular doses of 100,000 units of penicillin given every 8 hours are also shown for comparison. The reason for the difficulty in maintaining high plasma penicillin levels is readily apparent on examination of the penicillin plasma level curves. Increasing the penicillin dose from 100,000 units to a million units without giving caronamide increased the peak plasma penicillin

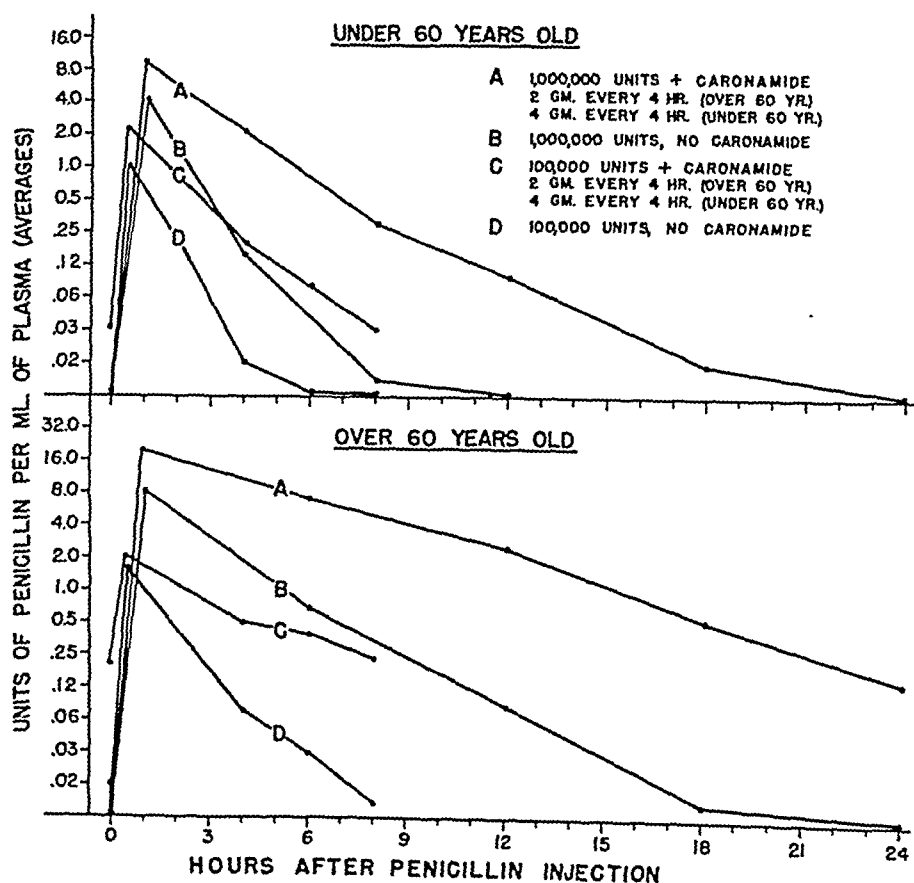


Figure 1. Plasma penicillin levels after intramuscular doses of penicillin with and without oral caronamide.

levels only 3- to 5-fold,\* and merely doubled the time during which penicillin was detected in the plasma. It is of interest that even in the older patients in whom, as previously noted,<sup>18</sup> penicillin excretion is somewhat delayed, the slopes of the blood level curves following the 100,000 and 1 million unit doses are identical. This finding suggests that the human tubular excretory mechanism is not saturated by as large a dose as 1 million units. In rabbits, Eagle and Newman<sup>9</sup> found that the tubular excretory mechanism could be saturated by single intravenous doses of 600 mg. of penicillin G per Kg. This corresponds to a dose of 60 million units in the average adult man.

High plasma penicillin levels can be maintained with relative ease by simultaneous administration of large doses of penicillin and caronamide. If the curves of the penicillin plasma levels shown in Figure 1 for both young and old people receiving 100,000 units of penicillin with caronamide are projected, they would actually cross the curves obtained with 1,000,000 units of penicillin without caronamide. Except during the first few hours, the penicillin plasma concentrations following the administration of caronamide are higher than those resulting from a 10-fold greater dose of penicillin without caronamide.

While other workers have reported that penicillin blood levels could be enhanced by administration of 2 gm. of sodium benzoate every 2 or 3 hours, none of the 4 patients in this experiment receiving a similar dosage showed significant enhancement of their penicillin levels. Furthermore, only 1 of 4 patients who received the larger amounts of sodium benzoate showed definite elevation of penicillin levels as compared with control values. In this one patient 4.5 gm. of sodium benzoate every 2 hours proved less effective in enhancing penicillin plasma levels than did 2 gm. of caronamide given every 4 hours. While it is probable that penicillin levels could be further enhanced by increasing the sodium benzoate dosage, 3 patients complained of nausea with the dosage used.

**Conclusions.** The oral administration of caronamide together with large intramuscular doses of penicillin makes it possible to maintain high penicillin plasma levels with relative ease. The effect of caronamide in prolonging penicillin plasma levels is greater than that resulting from a 10-fold increase in the penicillin dosage. Sodium benzoate in 4 patients was found to be much less effective than caronamide in enhancing penicillin levels.

\* The differences may have been somewhat greater since the "peak" level in the present study was determined at 1 hour whereas in the previous study it was taken at  $\frac{1}{2}$  hour.

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# PLASMA PENICILLIN LEVELS AFTER ORAL PENICILLIN WITH AND WITHOUT ORAL CARONAMIDE\*†

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It is generally assumed, though by no means established, that penicillin therapy to be effective, should provide suitable concentrations of the antibiotic throughout the interval between doses. Because of its rapid renal excretion and the vagaries of its absorption from the gastrointestinal tract, some simple and effective method of enhancing and prolonging penicillin levels during its oral administration would seem desirable. It has been shown that caronamide (4'-carboxyphenylmethanesulfonanilide) inhibits reversibly the renal tubular excretion of penicillin,<sup>1,2</sup> and when given by mouth, enhances and prolongs the plasma penicillin levels resulting from parenterally administered penicillin.<sup>3,4,6,12-15</sup> Studies on the effect of caronamide on the blood levels obtained during oral penicillin administration are the subject of this report.

**Materials and Methods.** The subjects were all convalescent adult male patients who had no definite evidence of renal damage, congestive failure, or other serious illness. Both young and old men

were studied. The routine of the hospital was not disturbed. Diets, fluids and salt intake were not altered. Meals were served on the hospital schedule, namely, at 7 and 11 a.m. and 4 p.m. Medications (caronamide and penicillin) were timed to the routine 4-hourly hospital schedule (9-1-5) and measures were taken to administer the drugs promptly and with certainty.

Tablets (supplied by Commercial Solvents Corporation) each containing 100,000 units of crystalline potassium penicillin G, buffered with 0.5 gm. sodium citrate were used exclusively. One tablet was given every 4 hours beginning at 9 a.m. of day 1, and continued through 5 p.m. of day 4. Blood samples were drawn before, during and after the caronamide administration at such intervals as to provide several observations of the 4-hour level, just prior to taking the next tablet of penicillin, as well as a series of levels taken at 45 minutes, 2 hours and 4 hours following a dose. Each patient served as his own control before and after the caronamide administration. Penicillin concentrations were assayed on citrated plasma by the serial dilution method of Kammellkamp,<sup>6</sup> modified only by the use of 0.5 ml. of the plasma dilutions.

Caronamide\* was given by mouth in the form of tablets that were finely ground and then suspended in chocolate flavored milk with the aid of a Waring blender. The first dose of caronamide was given at 1 p.m. of day 2, with doses repeated every 4 hours, at the same time as the penicillin, the final dose being given at 1 p.m. of day 3. Plasma penicillin levels between penicillin doses were obtained before the first and last doses of caronamide and again 20 hours after the last dose of caronamide. The caronamide was employed in 3 different dosages: one group of individuals under 60 years old received 4 grams every 4 hours, a second group over 60 years old was given 2 grams every 4 hours. These amounts had produced a satisfactory enhancing effect when penicillin was given intramuscularly.<sup>12,13</sup> A third group of patients over 60 years old was given 3 grams every 4 hours.

A method for determining plasma caronamide concentrations<sup>16</sup> became available before these studies were completed. This method with minor modifications was used to study the blood caronamide concentrations in the last group of patients (those over 60, receiving 3-gram doses of caronamide).

**Results.** The findings will be presented separately for each of the 3 groups of patients.

*Group 1.* Eight patients under 60 years old received 4 gm. of caronamide every 4 hours. The plasma penicillin levels before, during and after the caronamide administration in each of these patients and the averages for the group are shown in Table 1. These levels varied somewhat in different individuals during the control periods and while caronamide was being given, both 4 hours after the penicillin doses and in the interval between doses. With one exception the levels obtained before and after the caronamide were essentially the same. In Patient 8 they were substantially higher in the

postcaronamide than in the precaronamide control period.

The average levels obtained 4 hours after a dose of penicillin in the different patients ranged from 0.01-0.08 units before and from 0.01-0.06 units after caronamide was given. During the caronamide the corresponding levels ranged between 0.02 and 0.20 units. The average level for the 8 patients 4 hours after a dose of penicillin was about  $2\frac{1}{2}$  times higher during caronamide administration than in the control periods. There was a similar enhancement in the average penicillin levels 45 minutes and 2 hours after a dose.

In the control periods before and after caronamide administration, more than one-fourth of the plasma specimens obtained 4 hours after a dose of penicillin showed no demonstrable penicillin activity, and three-fourths of such specimens yielded levels of 0.02 units or less. During the caronamide period, on the other hand, penicillin activity was detectable in all but 1 specimen and almost three-fourths of the specimens obtained 4 hours after a dose yielded concentrations of 0.03 or higher.

*Group 2.* There were 9 patients over 60 years old in this group and each was given 2 gm. of caronamide every 2 hours. The penicillin levels obtained in this group are shown in Table 2. The results were quite irregular. Levels of 0.03 units per ml. or higher were maintained during the control periods in most of these patients. The average of all the levels obtained 4 hours after a dose was about 0.07 units per ml. during the control periods and 0.12 units per ml. during caronamide administration. Enhancement of penicillin levels throughout most of the caronamide period was noted in only 2 patients (numbers 9 and 14).

\* Supplied by Sharp & Dohme, Inc., through the courtesy of Dr. William P. Boger.



TABLE 1. PLASMA PENICILLIN LEVELS IN PATIENTS UNDER 60 YEARS OF AGE, RECEIVING 100,000 UNITS BY MOUTH EVERY 4 HOURS, WITH OR WITHOUT ORAL CARONAMIDE, 4 GRAMS EVERY 4 HOURS\*

Patient	Age	NPN**	Caron- amide Grams Every 4 Hours	Day	Hours After Preceding Penicillin Dose							
					4 (9 pm)	4 (9 am)	$\frac{3}{4}$ (9:45 am)	2 (11 am)	4 (1 pm)	4 (5 pm)	4 (9 pm)	Aver- age §
1	36	35	0	1					0.03	0.02		
			0	2		0.02	0.06	0.06	0.02			0.02
			4	3	0.06#	0.05	0.12	0.12	0.03	0.02		0.04
			0	4		0.02	0.06	0.06	0.03	0.02	0.02	0.02
2	52	36	0	1					0	0		
			0	2		0.01	0.02	0.06	0.02			0.01
			4	3	0.02#	0.03	0.25	0.09	0.02	0.02		0.02
			0	4		0.02	0.06	0.12	0	0	0	0.01
3	41	32	0	1					0.03			
			0	2		0.03	0.06	0.02	0			0.02
			4	3	0.01#	0.03	0.12	0.12	0.06	0.02		0.03
			0	4		0.02	0.12	0.01	0.02	0	0	0.01
4	30	26	0	1					0.02	0.02		
			0	2		0.02	0.25	0.06	0			0.02
			4	3	0.02#	0.03	1.0	0.25	0.03	0.03		0.03
			0	4		0.02	0.25	0.03	0.02	0	0	0.01
5	43	23	0	1					0.06	0.12		
			0	2		0.06	0.12	0.12	0.06			0.08
			4	3	0.06#	0.25	0.38	0.5	0.25	0.25		0.20
			0	4		0.06	0.25	0.25	0.06	0.06	0.06	0.06
6	53	33	0	1					0.02	—		
			0	2		0.02	0.06	0.06	0.02			0.02
			4	3	0#	0.06	0.12	0.06	0.06	—	—	0.04
			0	4		0.03	0.03	0.03	0.03	0	0	0.02
7	45	—	0	1					0	0		
			0	2		0.02	0.12	0.03	0			0.01
			4	3	0.02#	0.12	0.25	0.12	0.06	0.06		0.07
			0	4		0.02	0.12	0.12	0.02	0	0	0.01
8	45	28	0	1					—	—		
			0	2		0.03	0.06	0.12	0.03			0.03
			4	3	0.06#	0.06	—	0.25	0.12	0.12		0.09
			0	4		0.12	0.25	0.25	0.06	0.02	0.02	0.06
Average 1-8	43	30	0	1					0.02	0.03		
			0	2		0.03	0.09	0.07	0.02			0.03
			4	3	0.03#	0.08	0.32	0.19	0.08	0.08		0.07
			0	4		0.04	0.14	0.11	0.03	0.01	0.01	0.02

\* The penicillin was started at 9 a.m. on day 1; the first dose of caronamide was given at 1 p.m. on day 2 and the last dose at 1 p.m. on day 3.

\*\* Average of values before, during and after caronamide administration.

# Blood drawn on day 2, 8 hours after caronamide was started.

§ The first value listed for each subject is the average of the levels obtained 4 hours after a dose on days 1 and 2 before caronamide was started; the second is the average of the 4-hour levels during, and the third after caronamide.

— = not done.

TABLE 2. PLASMA PENICILLIN LEVELS IN PATIENTS OVER 60 YEARS OF AGE, RECEIVING 100,000 UNITS BY MOUTH EVERY 4 HOURS, WITH OR WITHOUT ORAL CARONAMIDE, 2 GRAMS EVERY 4 HOURS\*

Patient	Age	NPN**	Caron- amide Grams Every 4 Hours	Day	Hours After Preceding Penicillin Dose							
					4 (5 pm)	4 (9 am)	3/4 (9:45 am)	2 (11 am)	4 (1 pm)	4 (5 pm)	4 (9 pm)	4 Aver- age §
9	>80	28	0	1					0.12	0.12		
			0	2		0.03	0.12	0.25	0.12			0.10
			2	3	0.12#	0.02	0.25	0.25	0.25	0.4		0.20
			0	4		0	0.09	0.03	0.06	0.06	0.06	0.05
10	90	38	0	1					0.03	0.02		
			0	2		0	0.09	0.06	0.02			0.02
			2	3	0.03#	0	0.02	0.02	0.01	0.06		0.03
			0	4		0	0.02	0.02	0	0.02	0.02	0.01
11	75	33	0	1					0.03	0.02		
			0	2		0.06	0.03	0.25	0.03			0.04
			2	3	0.03#	0	0.06	0.12	0.03	0.03		0.02
			0	4		0	0.06	0.06	0.02	0.02	0.02	0.02
12	76	38	0	1					0.06	0.06		
			0	2		0.12	0.12	0.25	0.12			0.09
			2	3	0.12#	0.12	0.12	0.12	0.06	0.25		0.14
			0	4		0.02	0.06	0.03	0.06	0.03	—	0.04
13	82	38	0	1					0.03	0.02		
			0	2		0.02	0.02	0.02	0.02			0.02
			2	3	0.03#	0.01	0.09	0.06	0.02	0.03		0.02
			0	4		0.02	0.06	0.06	0	0.02	—	0.01
14	66	38	0	1					0.01	0.01		
			0	2		0.06	0.12	0.06	0.02			0.03
			2	3	0.02#	0.20	0.25	0.25	0.06	0.03		0.08
			0	4		0.03	0.06	0.12	0.02	0.02	—	0.02
15	79	37	0	1					0.03	0		
			0	2		0.06	0.12	0.12	0.03			0.03
			2	3	0.03#	0.06	0.25	0.12	0.03	0.03		0.04
			0	4		0.06	0.12	0.12	0.03	0.02	—	0.04
16	69	40	0	1					0.03	0.03		
			0	2		0.03	0.03	0.06	0.02			0.03
			2	3	0.03#	0.02	0.02	0.03	0.03	0.02		0.03
			0	4		0	0.02	0.02	0	0	—	0
17	83	45	0	1					0.12	0.12		
			0	2		0.12	0.50	1.0	0.25			0.15
			2	3	0.50#	0.5	0.50	0.5	0.25	1.0		0.56
			0	4		1.0	1.0	1.0	0.50	0.12	—	0.54
Average 9-17	78	37	0	1					0.05	0.04		
			0	2		0.06	0.13	0.23	0.07			0.06
			2	3	0.10#	0.10	0.17	0.16	0.08	0.20		0.12
			0	4		0.13	0.17	0.16	0.08	0.03	0.03	0.08

\* The penicillin was started at 9 a.m. on day 1; the first dose of caronamide was given at 1 p.m. on day 2, and the last dose at 1 p.m. on day 3.

\*\* Average of values before, during and after caronamide administration.

# Blood drawn on day 2, 4 hours after initial dose of caronamide.

§ The first value listed for each subject is the average of the levels obtained 4 hours after a dose on days 1 and 2 before caronamide was started; the second is the average of the 4-hour levels during, and the third, after caronamide.

— = not done.

*Group 3.* In this group there were 7 patients over 60 years old who received 3 gm. of caronamide every 4 hours and their penicillin levels are shown in Table 3. In these patients, as in those of Group 2, concentrations of 0.03 units per ml. were obtained during almost the entire control periods before and after caronamide was given. Enhancement of the plasma penicillin levels throughout most or all of the period of caronamide administration occurred in every one of these patients. The average of all the levels obtained 4

TABLE 3. PLASMA PENICILLIN LEVELS IN PATIENTS OVER 60 YEARS OF AGE, RECEIVING 100,000 UNITS BY MOUTH EVERY 4 HOURS, WITH OR WITHOUT ORAL CARONAMIDE, 3 GRAMS EVERY 4 HOURS\*

Patient	Age	NPN**	Caronamide Grams Every 4 Hours	Hours After Preceding Penicillin Dose						
				Day	4 (5 pm)	4 (9 am)	4 (9:45 am)	2 (11 am)	4 (1 pm)	4 (5 pm)

18	74	36	0	1	0.02	0.02	0.02	0.02	0.02	0.04
			0	2	0.02	0.03	0.03	0.06	0.12	0.09
			3	3	0.06#	0.12	0.25	0.25	0.12	0.11
			4	4	0.06	0.06	0.06	0.12	0.12	0.08

19	78	33	0	1	0.02	0.02	0.02	0.02	0.02	0.04
			0	2	0.03	0.03	0.03	0.04	0	0.09
			3	3	0.03#	0.12	0.25	0.12	0.06	0.10
			4	4	0.06	0.06	0.06	0.12	0.06	0.05

20	74	29	0	1	0.03	0.03	0.03	0.03	0.03	0.05
			0	2	0.06	0.12	0.12	0.06	0.06	0.05
			3	3	0.20#	0.50	0.50	0.25	0.20	0.30
			4	4	0.06	0.06	0.12	0.12	0.06	0.08

21	62	50	0	1	0.03	0.12	0.12	0.12	0.12	0.10
			0	2	0.08	0.12	0.12	0.12	0.09	0.08
			3	3	0.12#	0.80	0.50	0.50	0.50	0.39
			4	4	0.12	0.12	0.12	0.25	0.12	0.12

22	73	42	0	1	0.06	0.12	0.12	0.12	0.06	0.08
			0	2	0.09	0.12	0.12	0.12	0.09	0.08
			3	3	0.12#	0.80	0.50	0.50	0.50	0.39
			4	4	0.12	0.12	0.12	0.25	0.12	0.12

23	83	56	0	1	0.03	0.03	0.03	0.03	0.03	0.04
			0	2	0.06	0.12	0.12	0.12	0.06	0.08
			3	3	0.06#	0.06	0.12	0.20	0.12	0.08
			4	4	0.40	0.40	0.25	0.25	0.12	0.21

24	80	43	0	1	0.02	0.02	0.02	0.02	0.02	0.05
			0	2	0.05	0.20	0.20	0.20	0.05	0.05
			3	3	0.06#	0.06	0.25	0.50	0.25	0.17
			4	4	0.20	0.20	0.50	0.25	0.12	0.12

Average	75	41	0	1	0.03	0.03	0.03	0.03	0.03	0.05
			0	2	0.08	0.11	0.11	0.39	0.24	0.19
			3	3	0.10#	0.28	0.30	0.39	0.14	0.19
			4	4	0.13	0.20	0.20	0.19	0.08	0.09

\* The penicillin was started at 9 a.m. on day 1; the first dose of caronamide was given at 1 p.m. on day 2, and the last dose at 1 p.m. on day 3.  
 \*\* Average of values before, during and after caronamide administration.  
 # Blood drawn on day 2, 4 hours after initial dose of caronamide.  
 § The first value listed for each subject is the average of the levels obtained 4 hours after a dose on days 1 and 2 before caronamide was started; the second is the average of the 4-hour levels during caronamide and the third, after caronamide.

TABLE 4. PLASMA CARONAMIDE LEVELS IN THE PATIENTS LISTED IN TABLE 3.

			Plasma Caronamide, Mg. per 100 Ml.									
			Day 2		Day 3					Day 4		
			9 am	5 pm	9 am	9:45 am	11 am	1 pm	5 pm	9 am	1 pm	5 pm
Patient	Age	NPN*	Hours After Previous Dose of Caronamide									
			Before	4	4	3/4	2	4	4	20	24	28
18	74	36	0	14	15	18	28	18	17	2	1	<1
19	78	33	0	13	15	16	17	19	26	2	<1	<1
20	74	29	0	15	16	31	29	27	26	1	<1	<1
21	62	50	0	21#	37	45	45	35	42	>10	>10	10
22	73	42	0	16	31	28	35	35	36	18	15	14
23	83	56	0	16	36	—	41	35	41	27	20	20
24	80	43	0	17	29	36	28	27	37	34	14	13
Averages												
18-20	75	33	0	14	15	22	25	21	23	2	<1	<1
21-24	75	48	0	18	33	36	37	33	39	>22	>15	14
18-24	75	42	0	16	26	29	32	28	32	13	9	8

\* Average of the values obtained before, during and after the caronamide administration.

# Initial caronamide dose in this patient was 6 grams. Penicillin tablets by mouth, 100,000 units every 4 hours, started at 9 a.m. on day 1 and continued through 5 p.m. on day 4. Caronamide, 3 grams every 4 hours orally, started at 1 p.m. on day 2 and discontinued after the 1 p.m. dose on day 3.

hours after the penicillin doses was 0.05 units per ml. in the precaronamide period as compared with 0.19 units per ml. while caronamide was being given, an almost four-fold increase attributable to the caronamide.

The penicillin levels in the postcaronamide period were essentially the same as in the precaronamide period in Patients 18, 19, 20 and 21, but in the 3 remaining patients the postcaronamide levels were higher than those obtained before the caronamide was begun. Indeed, in Patients 23 and 24 penicillin levels were even higher for some time after the caronamide was stopped than they were at corresponding times while they were taking the adjuvant.

*Plasma Caronamide Levels in Group 3.* The individual differences just noted suggested the possibility that variations in the absorption and excretion of caronamide in the several patients might account for the discrepancies. Caronamide determinations were, therefore, carried out in this group of patients.

The results are shown in Table 4.

The plasma caronamide concentrations were lower in Patients 18, 19 and 20 than in the 4 remaining patients throughout the period of caronamide administration. In addition, only traces of caronamide were still present 20-28 hours after the last dose in the former, while substantial concentrations were still present at that time in the latter. The average age of the patients was the same in the 2 groups but the blood nonprotein nitrogen levels were higher in those who maintained the high levels of caronamide after that drug was discontinued. Three of the latter, but none of the former patients showed high plasma penicillin levels in the postcaronamide period.

*Average Levels.* The average plasma penicillin levels obtained 4 hours after some of the doses of penicillin and in the interval between penicillin doses during caronamide administration and during the control periods are shown graphically for each of the 3 groups of patients in Figure 1. The enhancing

effect of caronamide both on the 4-hour levels as well as on the levels obtained between penicillin doses in Groups 1 and 3 can be seen clearly. The average caronamide levels in Group 3 are also shown in this figure.

*Frequency with Which Various Plasma Penicillin Levels were Maintained.* Since the oral doses of penicillin were given at 4-hourly intervals, the height of the penicillin levels obtained at the end of these intervals should afford the best reflection of the enhancing and prolonging effect of the caronamide.

The frequency with which various penicillin concentrations were attained at this time during caronamide administration and in the 2 control periods is shown graphically for each of the 3 groups of patients in Figure 2. The enhancing effect of the caronamide in Groups 1 and 3 is indicated by the significantly greater proportion of the higher concentrations during caronamide administration. The distribution of the penicillin levels in the pre- and post-caronamide control periods was essentially the same in Group 1, where-

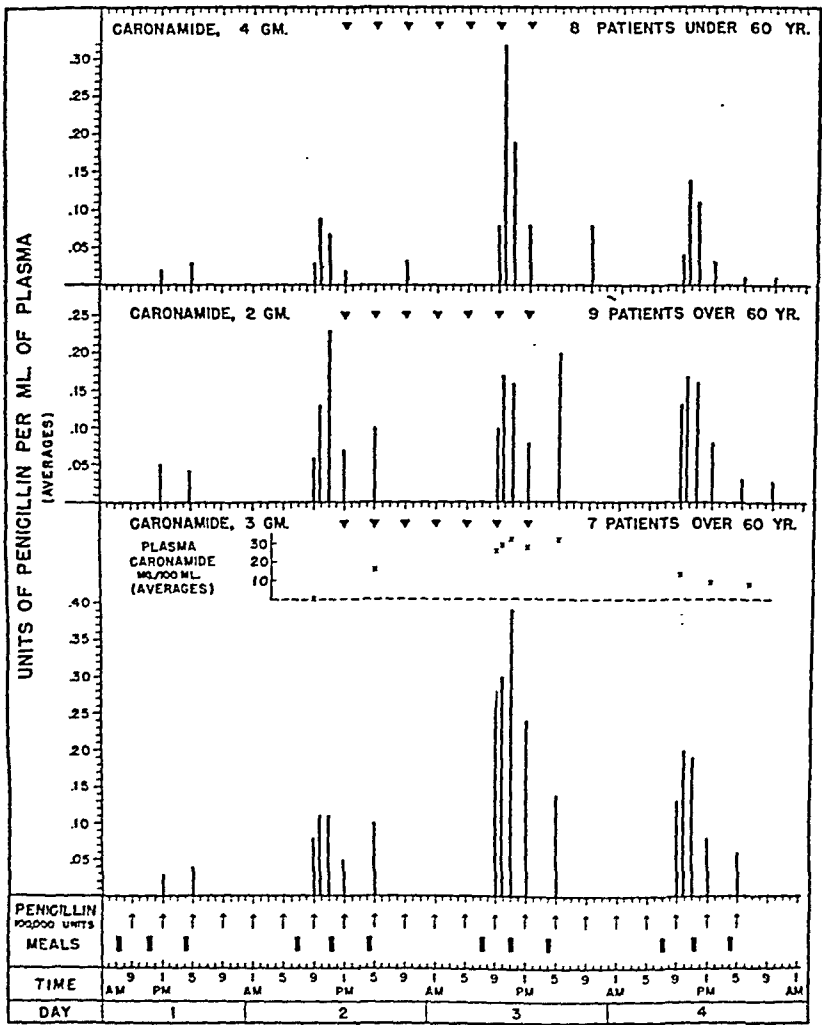


Figure 1. Average plasma penicillin levels resulting from oral doses of 100,000 units of penicillin given every 4 hours before, during and after oral caronamide administration in 3 groups of patients. The average plasma caronamide levels for one of these groups are also shown. The solid triangles indicate the time when caronamide doses were given.

as in Group 3 the distribution of the levels in the postcaronamide period was intermediate between that of the caronamide period and the one for the precaronamide controls. The distribution curves for Group 2 were irregular.

**Toxicity.** There were no significant toxic symptoms, abnormal urinary findings or rises in blood nonprotein nitrogen levels during caronamide therapy in any of these patients.

**Comment.** The data presented confirm the findings of other workers<sup>4,14,15</sup> and indicate that oral caronamide in sufficient amounts has an enhancing

effect on plasma penicillin levels when the penicillin is given orally. This enhancing effect seems to be less marked than was the case when penicillin was given intramuscularly.<sup>12,13</sup> Furthermore, the effects of caronamide during oral penicillin appear to be more erratic and the individual variations as shown, in Tables 1-3, are even greater than when penicillin is given intramuscularly.

In the case of oral penicillin, one must consider first the factors of absorption and of excretion.<sup>5,7,8</sup> Absorption of penicillin when given orally is considerably more irregular than when

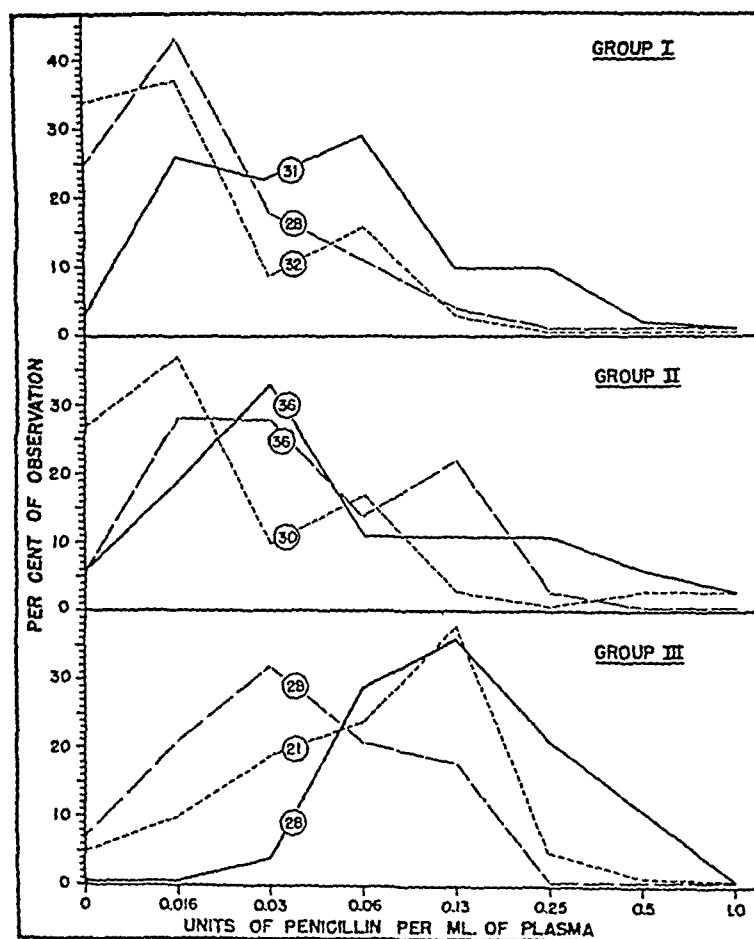


Figure 2. Frequency with which various plasma penicillin concentrations (complete inhibition) were obtained 4 hours after oral doses of 100,000 units of penicillin before (coarsely broken line), during (solid line), and after (finely broken line) caronamide administration. The numbers of observations are shown in the circles. Group 1: 8 patients under 60 years old; 4 gm. of caronamide every 4 hours (Table 1). Group 2: 9 patients over 60 years old; 2 gm. of caronamide every 3 hours (Table 2). Group 3: 7 patients over 60 years old; 3 gm. of caronamide every 4 hours (Table 3).

it is given intramuscularly.<sup>5,7</sup> The rate of excretion is also subject to individual variations and is especially influenced by age<sup>12,13</sup> and by the state of renal function.<sup>11</sup>

In the present study some of the factors influencing the blood levels obtainable from oral penicillin have been controlled as far as possible. Thus the effects of meals<sup>5</sup> were kept constant by giving them at the same time in relation to the doses of the drugs under study. The factor of gastric acidity<sup>5,10</sup> was not controlled except insofar as it varies with age. The renal function was not studied intensively but patients were chosen for these studies because they were thought to have essentially normal renal function as indicated by the failure to find abnormal elements in the urine, by good concentrating power and by the fact that the blood nonprotein nitrogen was essentially within the normal range as seen in patients in this age group at this hospital. The levels of nonprotein nitrogen, however, were slightly elevated in a few patients and these patients (numbers 17, 22, 23 and 24) showed evidence of persistence of elevated plasma levels of both penicillin and caronamide, presumably because of the delay in excretion.

That age alone has an enhancing and prolonging effect on penicillin blood levels when repeated doses of that antibiotic are given was shown in previous studies with intramuscular injections of large doses of penicillin.<sup>12,13</sup> This effect was confirmed in the present studies for patients receiving penicillin orally. Thus, while about three-fourths of the observations made 4 hours after oral doses during control periods in persons under 60 years old showed little or no demonstrable penicillin in the plasma, more than two-thirds of the corresponding observations made in older people showed

levels of 0.03 units per ml. or higher. Presumably, the same mechanism, namely reduction in the functional tubular excretory mass is responsible for this phenomenon and for the greater enhancing effect of caronamide. The latter is also reflected in the fact that in the old people a smaller dose of caronamide produced a greater prolongation and enhancement of penicillin levels than did the larger doses in the younger patients.

To be sure, the general assumption that it is necessary to maintain certain minimum concentrations of penicillin in the circulating blood in order to achieve an optimum therapeutic effect remains to be proved. Nevertheless, it seems reasonable to suppose that when the maximum levels achieved in the blood are the same, prolongation of high levels from the same dose is desirable from a chemotherapeutic point of view.

The few observations that were made on plasma caronamide concentrations in the patients of Group 3 indicate that absorption and/or excretion of orally administered caronamide varies in different individuals. The results obtained in these patients suggest that such variations may account for the differences in the enhancing and prolonging effect of the caronamide and for the duration of its effects.

In these studies, as in those previously reported from this laboratory,<sup>12,13</sup> caronamide was given for only 24 hours. It is of course not possible from such observations to draw conclusions as to the suitability of this agent for prolonged use in therapy.

**Summary and Conclusions.** Oral penicillin when administered alone in doses of 100,000 units every 4 hours could not be relied upon to maintain significant concentrations of the antibiotic in the plasma in persons under

60 years of age. Penicillin levels of 0.03 units per ml. were usually maintained in persons over 60 years old on the same dosage.

Caronamide in oral doses of 4 gm. every 4 hours in persons under 60 and in doses of 3 gm. every 4 hours in those over 60 enhanced and prolonged the levels from oral penicillin.

In patients older than 60 years with slightly elevated blood nonprotein nitrogen levels the enhancing effect of caronamide persisted for at least 28 hours after the caronamide was discontinued. This effect was associated with persistence of significant caronamide concentrations in the blood of these patients.

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# POLIOMYELITIS IN FAMILIES ATTACKED BY THE DISEASE I. DISTRIBUTION OF VIRUS IN STOOL AND OROPHARYNX OF MEMBERS IN HOUSEHOLDS.\*

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Present knowledge of the risk of attack among persons living in households in which poliomyelitis appears indicates that frequently several members of a family develop clinical or sub-clinical attacks of the disease<sup>10,12</sup> Aycock and Eaton<sup>1</sup> and later Casey *et al.*<sup>2</sup> studied multiple cases in families. Their studies indicated that simultaneous infection in family members is common, and that the source of virus in these outbreaks is closely related to the household. Pearson and associates<sup>11</sup> in an urban outbreak of poliomyelitis, found that carriers of virus were concentrated about those households in which there was a paralyzed patient. In these limited loci, apparently, there is a wide distribution of virus in humans.

The broad purpose of this report is to call attention again to the widespread distribution of poliomyelitis virus in certain households attacked by the disease. In a recent paper that appeared shortly before one of ours<sup>13</sup> Zintek<sup>14</sup> was able to demonstrate rapid dispersion of virus in a family within an 8 day period. He was able to conclude that poliomyelitis virus must have seated itself at almost the same time among the mem-

bers of this family, which is to say that each exposure was simultaneous at a common source. Our evidence is somewhat indirect compared with Zintek's but in general we are in agreement with his conclusions.

**Material and Methods.** *Clinical material.* A widespread outbreak of poliomyelitis occurred in the state of Kansas during the summer of 1946.\*\* In eastern Kansas a large number of children and adults were referred to the University of Kansas Hospitals for diagnosis and treatment. The family histories obtained from some patients indicated that illness had occurred in additional family members. Among these households 5 were visited and samples of stool, oropharyngeal exudate and whole blood were obtained from each member of the family. (a) *Stools.* Individual stool samples were collected within a few days. The manner of collection of stools has been described.<sup>14</sup> Less than 12 hours elapsed after stools were collected and storage of them in a dry ice cabinet. (b) *Throat swabs.* The oropharynx of each patient was swabbed at the time of admission to the hospital. During the ensuing few days (1 to 7) the throat of each member in the household was sampled. Two or four cotton pledgets on applicator sticks were used to collect exudate from the oropharynx. Cotton pledgets were applied and rapidly

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moved in order that tonsillar tissue and mucosa of the palatine fossa was gently rubbed. The cotton moistened with exudate was placed in individual sterile screw-capped bottles containing 1 cc. of distilled water. Specimens were stored promptly in a dry ice box.

*Preparation of Inoculum.* (a) *Stools.* The method of preparation of stool extract for intranasal and intraperitoneal inoculation of a monkey has been described.<sup>6,13</sup> Penicillin (50,000 units) was added to the etherized fraction 20 minutes prior to inoculation. (b) *Throat swabs.* In the test for virus, thawed cotton pledgets representing an individual sampling were moistened with 0.3 cc. of glycine acetate phosphate (GAP) buffer at pH 8.2. These pledgets were placed in a sterile 5 cc. syringe and the absorbed fluid expressed into a test tube. To this eluate 0.3 cc. of GAP buffer, pH 4.4, was added bringing the fluid to about pH 6.0.<sup>9,15</sup> Ether was added. The tube was shaken gently and placed in the ice box (6° C.) overnight. The tube was capped with a cotton plug to permit volatilization of the ether. Almost invariably the eluate fraction was free of bacteria.

*Inoculation.* (a) *Stools.* The combined intraperitoneal and intranasal portals were used for inoculation. Each monkey received 10 to 20 cc. of the etherized fraction once intraperitoneally. In addition, from 3 to 5 cc. of raw stool extract were instilled into the nasopharynx of the test animal on each of 5 consecutive days.<sup>6</sup> (b) *Throat swabs.* 0.4 or 0.5 cc. of the prepared eluate was inoculated into each thalamic area of a monkey.<sup>7</sup>

*Animals.*<sup>†</sup> *Macaca mulatta* (rhesus) and *Macaca irus* (cynomolgus) monkeys were used. Inoculated monkeys were observed twice daily. Daily temperature records were kept. Monkeys were sacrificed at an appropriate interval following the appearance of paralysis. The majority of the inoculated monkeys surviving 30 days were killed. A few were used a second time in other tests. Segments of

brain, midbrain, pons, medulla and spinal cord were preserved in formalin.

*Criteria for identification of poliomyelitis virus.* These have been described.<sup>16</sup> A positive test in this study indicates that the monkey developed paralysis and definitive lesions consistent with those seen in poliomyelitis were found in the spinal cord and elsewhere in the cerebral axis.

Several strains have been passaged in monkeys. None of these strains has produced illness in cotton rats, Swiss mice, guinea pigs, rabbits or hamsters.

*Results. A. Family studies.* There were 24 individuals living in 5 households. Of these persons, 17 had poliomyelitis virus in their intestinal excreta. Among these 17 persons, poliomyelitis virus was detected in the oropharynx of 7.

There were 14 children in these families (Table 2). All of the children had poliomyelitis, for virus was found in the stools of 13; the stool specimen from one child was not tested, for this patient had a paralytic attack. Poliomyelitis virus was detected in the oropharyngeal exudate obtained from each of 5 children.

Among 10 adults poliomyelitis virus was detected in stool samples obtained from 4; among these 4, virus was found in the oropharynx of two fathers. Poliomyelitis virus was not found in the remaining 6 adult members of 5 households which were studied.

The results of virus studies made on these individuals appear in Table 1. A brief summary of clinical data concerning the individuals in each household follows:

*Family T.P.* (Figure 1.) Residence—Olathe, Kansas. On July 5, 1946 the family spent a day at Wheeler Park in Seneca, Missouri. There, at the park, Mr. P. drank sulfur spring water. On

<sup>†</sup> Excepting the first 15 monkeys used in these tests, all others were tuberculin-tested using 10.0 mg. of human old tuberculin as the test dose. Only those monkeys providing a negative tuberculin test were used. *Rhesus* monkeys weighed between 2 and 7 kilograms; *cynomolgus* monkeys between 2 and 5 kilograms.

# MEMBERS OF FIVE HOUSEHOLDS OROPHARYNGEAL EXUDATE IN Date of Monkey

FIGURE 1. POST-ION POTOMAC VIRUS IN FEES AND OROPHARYNGEAL EXUDATE IN MEMBERS OF FIVE HOUSEHOLDS

Sex	Age (Years)	Type of Illness	Date of Monkey		Monkey No.	Fever	Paralysis		Histology
			Onset of Illness	Collected			Paralysis	Collected	
LP	M <sup>1</sup>	indefinite	7/10	8/3/46	R-119	0	0	8/3/46	C-128
	M <sup>2</sup>	none	8/4	8/4	R-123	0	0	8/3	R-103*
	F <sup>1</sup>	paralytic	7/25	8/8	R-120	105	9th day	8/3	R-88
	F <sup>2</sup>	paralytic	7/23	8/2	R-89	105	11th day	8/3	R-86
HM	M <sup>1</sup>	paralytic	7/23	8/2	R-112	105	12th day	8/3	R-102*
	F <sup>1</sup>	indefinite	8/2	8/2	R-91	104	11th day	8/3	R-87
	F <sup>2</sup>	indefinite	7/28	8/4	R-116	105 <sup>1</sup>	12th day	8/3	R-129
	M <sup>3</sup>	abortive	6/20	6/26/46	R-117	0	0	6/25	R-99*
CD	M <sup>1</sup>	abortive	6/20	6/25	R-122*	0	12th day	6/27	R-85
	M <sup>2</sup>	indefinite	6/22	6/25	R-113	106	24th day	6/27	R-90*
	M <sup>3</sup>	indefinite	6/17	6/25	R-90	105 <sup>1</sup>	12th day	6/27	R-101*
	M <sup>4</sup>	abortive	6/18	6/24	R-117	105 <sup>1</sup>	9th day	6/27	R-130
RC	M <sup>1</sup>	paralytic	6/17	6/25	R-115	105 <sup>1</sup>	14th day	7/31	R-104
	M <sup>2</sup>	abortive	6/15	6/25	R-121	105 <sup>1</sup>	11th day	7/26	R-99
	M <sup>3</sup>	abortive	6/15	6/25	R-124	105 <sup>1</sup>	7th day	7/31	R-94
	M <sup>4</sup>	none	7/31	7/31	R-109	104 <sup>1</sup>	18th day	8/19/46	C-132
FR	M <sup>1</sup>	indefinite	7/25/46	8/4	R-111	0	12th day	8/19	C-131
	M <sup>2</sup>	paralytic	7/29	8/4	R-118	0	0	8/17	R-97
	M <sup>3</sup>	indefinite	7/25/46	8/18/46	R-118	0	12th day	8/17	R-95
	M <sup>4</sup>	indefinite	7/21	7/21	R-122	106	18th day	7/18	C-135
M <sup>5</sup>	M <sup>1</sup>	paralytic	8/11	8/18	R-110	104 <sup>1</sup>	12th day	7/24/46	C-133
	M <sup>2</sup>	paralytic	8/13	8/18	R-114	106 <sup>1</sup>	0	0	0
	M <sup>3</sup>	paralytic	7/10/46	7/24/46	R-119	0	0	0	0
	M <sup>4</sup>	indefinite	7/10/46	7/24/46	R-138	0	0	not done	7/24
M <sup>6</sup>	M <sup>1</sup>	indefinite	7/21	7/21	R-123	0	0	7/25	R-125
	M <sup>2</sup>	indefinite	7/21	7/21	R-139	0	0	7/25	R-125
	M <sup>3</sup>	indefinite	7/21	7/21	R-122	106	18th day	7/18	C-135
	M <sup>4</sup>	indefinite	7/21	7/21	R-122	106	18th day	7/18	C-135

\* Monkey used again in another test, and susceptible to heterologous strain isolated during 1940 outbreak of poliomyelitis.  
 \*\* Temperature not taken.  
 C. M. inv. R. M. inv.

July 10 he developed an illness which lasted 3 days. His illness was characterized by fever ( $101^{\circ}$  F.), vomiting and diarrhea. On July 23, Melinda, *aet.* 10 years, complained of sore throat. She had fever ( $101.5^{\circ}$  F.) also. On July 25 she had headache and vomited. A stiff neck and weakness of both arms were found on July 28. She was then admitted to the hospital. There were 875 white cells/mm<sup>3</sup>

groups in the right leg. Melanie, *aet.* 4 years, and Tom, *aet.* 3 years, each had a day of illness marked by soreness of the arms and legs (July 25-Aug. 1). Mrs. P. was in attendance daily at the hospital. She did not have a recognized illness during the summer.

In summary, each child in this household had a recognized illness. Each of these illnesses occurred during a 7-

## T P FAMILY

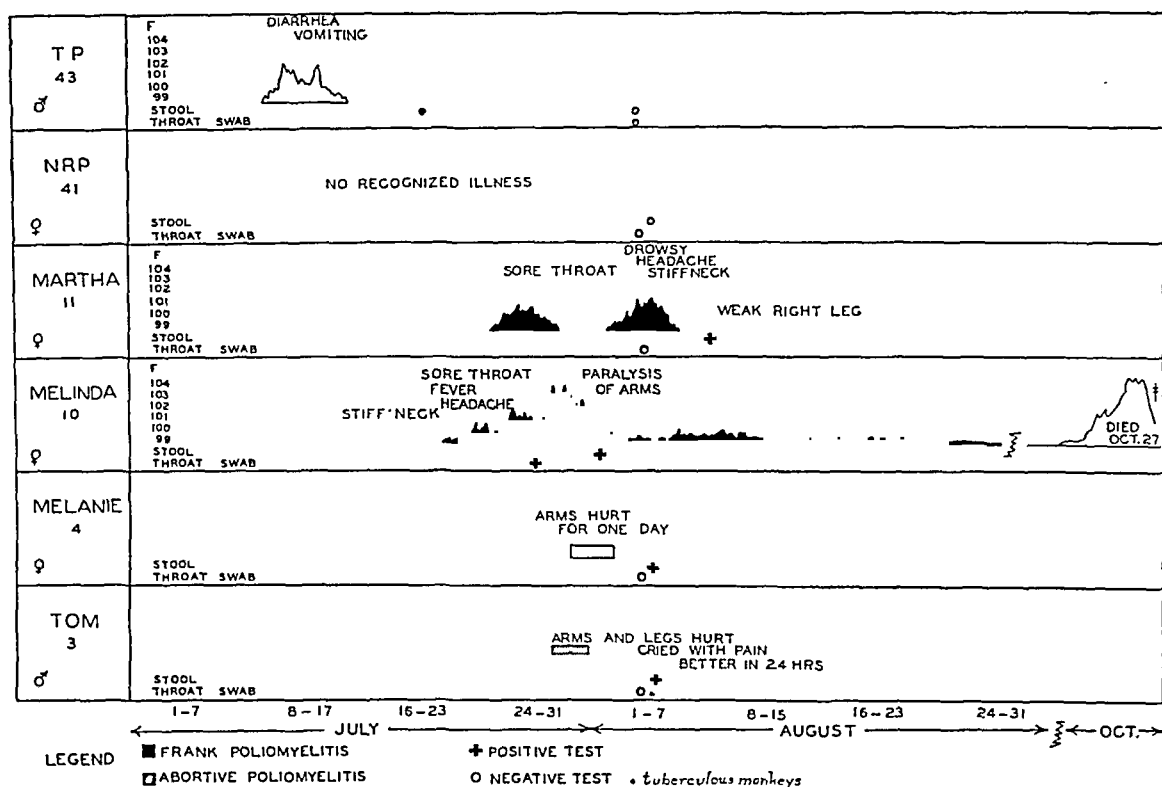


Fig. 1. Schematic diagram of T.P. Family.

The horizontal lines represent different individuals of the family; their ages and sex appear on the left hand side of the figure. The black area indicates the time of onset and course of a paralytic attack of poliomyelitis; the shaded area indicates the time of onset and course of an abortive attack of poliomyelitis; the open area indicates a minor poorly defined illness. The + and 0 marks are placed at the time the sampling of stool and throat was done.

in the cerebrospinal fluid; 95% of these were lymphocytes. Paralysis advanced to involve the respiratory muscles and after a stormy course of illness the patient died on Oct. 27, 1946. On July 25, Martha, *aet.* 11 years, had sore throat and fever ( $101^{\circ}$  F.). On August 3 she was drowsy and complained that her head ached. Her neck was stiff also. Subsequently Dr. G. M. Martin, of the department of physical medicine, found weakness of muscle

day period. Poliomyelitis virus was detected in the stool sample obtained from each child and in the oropharynx of the fatal case. The detection of poliomyelitis virus in the excreta of 2 siblings who had minor illnesses indicates that they had poliomyelitis. The brief period during which onset of illness occurred in these children suggests exposure to virus at a single source.

H M FAMILY

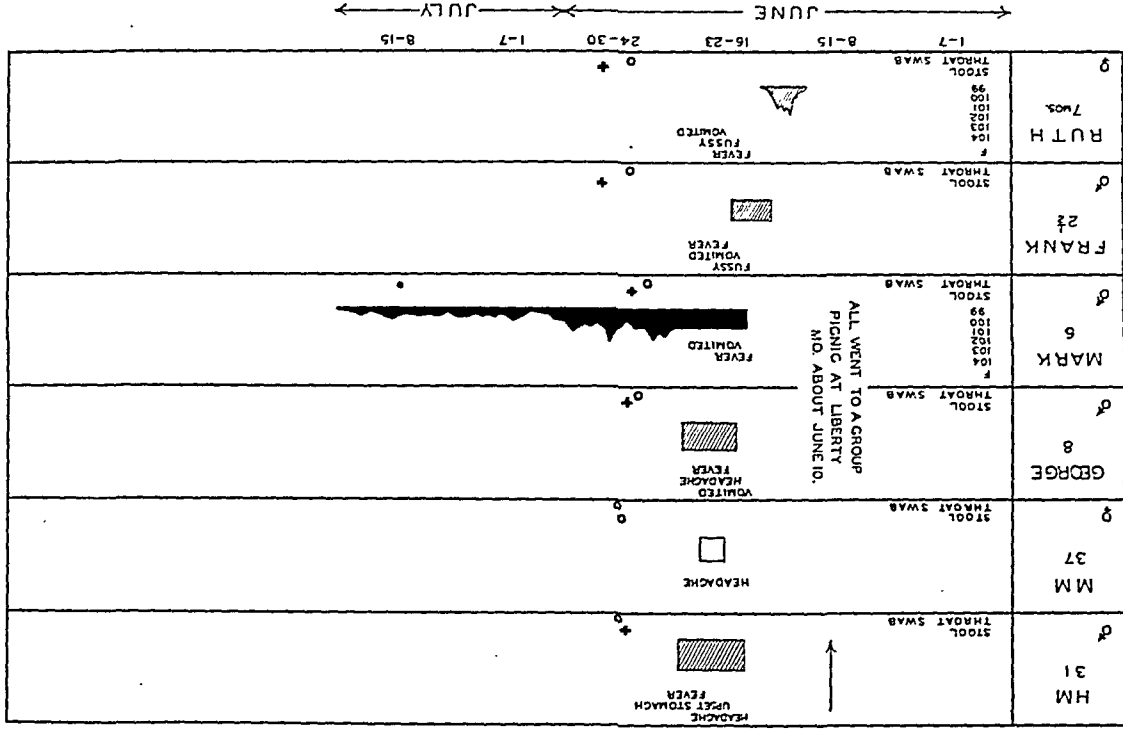


Fig. 2. Schematic diagram of H.M. Family.

The horizontal lines represent different individuals of the family, their ages and sex appear on the left hand side of the figure. The black area indicates the time of onset and course of a paralytic attack of poliomyelitis; the shaded area indicates a minor poorly defined illness. The + and 0 marks are placed at the time the sampling of stool and throat was done.

C D FAMILY

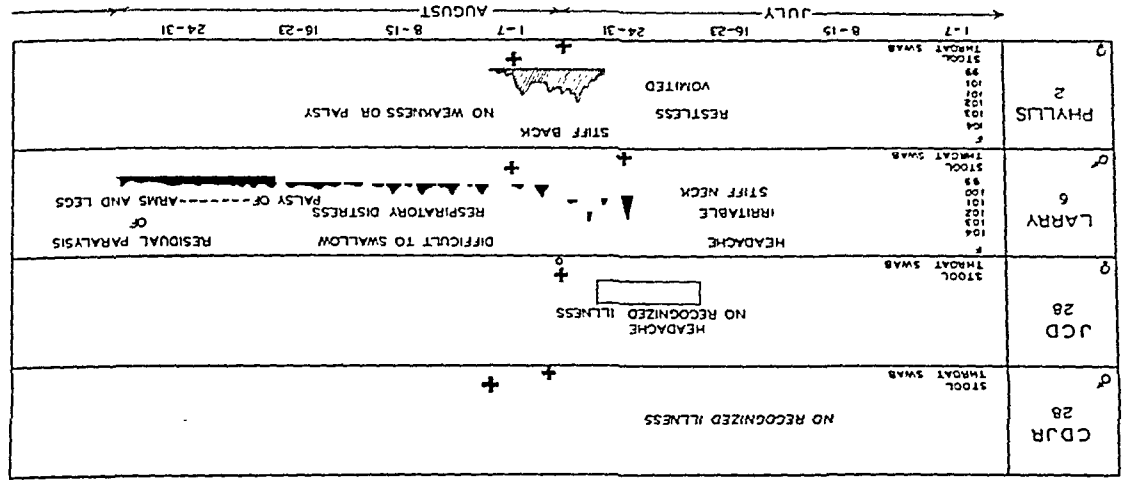


Fig. 3. Schematic diagram of C.D. Family.

The horizontal lines represent different individuals of the family, their ages and sex appear on the left hand side of the figure. The black area indicates the time of onset and course of a paralytic attack of poliomyelitis; the shaded area indicates a minor poorly defined illness. The + and 0 marks are placed at the time the sampling of stool and throat was done.

*Family H. M.* (Figure 2.) Residence—Kansas City, Missouri. On about June 10, 1946 this family went on a picnic at Liberty, Mo. On June 15, Ruth, *aet.* 7 months, was fussy, vomited and had fever ( $102^{\circ}$  F.). She recovered promptly. On June 17, Frank, *aet.*  $2\frac{1}{2}$  years, felt hot; he was fussy and vomited. George, *aet.* 8 years, on June 18 complained of headache. He vomited also. On the same day Mark, *aet.* 6 years, had fever and vomited. These symptoms persisted until June 22 when he regurgitated fluid through his nose when he swallowed. He was admitted to the hospital where weakness of muscles of the pharynx and left arm was found. There were 66 lymphocytes/mm<sup>3</sup> in the cerebrospinal fluid. Mr. M. became ill on June 20. He had headaches and an "upset stomach," although he did not vomit. He felt that he had fever. His illness lasted 2 days. Mrs. M. had headache on June 22; no other symptoms appeared.

In summary, each member in this household had a recognized illness. If Mrs. M. is excluded, each of these illnesses occurred within a 5-day period. Poliomyelitis virus was detected in the stool sample obtained from each child and from the father.

The presence of virus in the stool obtained from the siblings and father of the paralyzed patient indicates that each of these minor illnesses was poliomyelitis. The short interval of time in which onset of illness occurred in the members of this household suggests exposure to virus at a single source. Poliomyelitis virus was not detected in the oropharynx of any member of this household.

*Family C.D.* (Figure 3.) Residence—Osawatomie, Kansas. The children, Larry and Phyllis, played with three children in the McK. family, 2 of whom had clinically apparent poliomyelitis. An abstract of the McK. family history follows:

J. McK., *aet.* 8 years,—onset 7/21/46—meningeal type, abortive

Z. McK., *aet.* 5 years,—onset 7/21/46—bulbar, fatal

L. McK., *aet.* 2 years,—onset 7/23/46—abortive.

Virus isolation studies were not done with members of the McK. family.

On July 25, 1946 Larry D., *aet.* 6 years, had headache, stiff neck and back, and fever ( $103^{\circ}$  F.). He was admitted to the hospital where he developed paralysis of arms and legs. He also had difficulty in swallowing. There were 165 cells/mm<sup>3</sup> in the cerebrospinal fluid; 60% of these were lymphocytes. On July 29, Phyllis D., *aet.* 2 years, was restless. She vomited also. Her mother stated she felt "hot." On admission to the hospital she had fever ( $103^{\circ}$  F.) and a stiff back. The spinal tap revealed bloody fluid. There were 429 WBC and 529 RBC/mm<sup>3</sup> of spinal fluid; 23% of the white cells were lymphocytes. Phyllis did not develop demonstrable paralysis. Mr. D., *aet.* 28 years, was discharged from the Army on June 4, 1946. He worked as a laborer on the railroad and stated that during the month preceding illness in the children he was tired and had experienced generalized aches and pains. Mrs. D., *aet.* 28 years, had headache which lasted for 3 days (July 23-26).

In summary, 2 children and probably one adult in this family had a recognized illness. Each of these illnesses occurred during a 6 day period. Poliomyelitis virus was detected in the stool samples of each of 4 members of this household and in the oropharynx of 3 of these. Poliomyelitis attacked every member of this family. As in preceding households the brief period ensuing between onset of illnesses in 3 members suggests exposure at a common source. The presence of virus in the oropharynx of Mr. D. was regarded as meaning that he acquired his sub-clinical infection at about the same time as did the others in his family.

Considering the onset of illness in members of the McK. and D. families (within an 8-day period) it is not beyond peradventure that poliomyelitis virus entered into both family groups at the same time and from a common

source. If the premise that all members of the D. family acquired poliomyelitis at a common source is correct, then it appears unlikely that any member of the McK. family personally introduced virus into the D. household and that a vehicle served as the com-

mon carrier in the environment of both families. In other words, the 8-day period between onsets of illnesses as they occurred among the 9 members in these families is the variation one might expect in the incubation time.

*Family R.C. (Figure 4.) Residence—*

## R C FAMILY

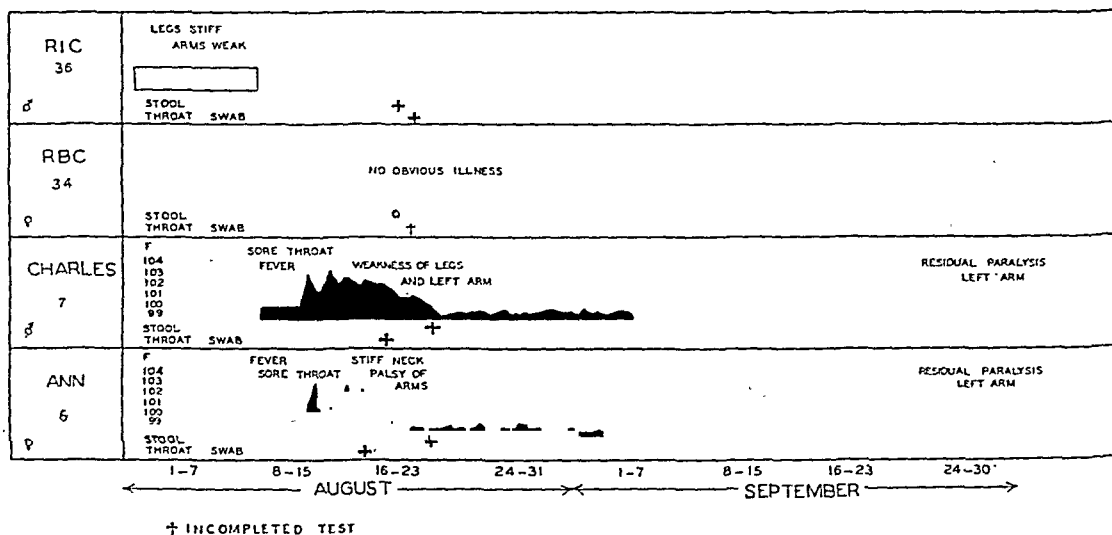


Fig. 4. Schematic diagram of R.C. Family.

The horizontal lines represent different individuals of the family; their ages and sex appear on the left hand side of the figure. The black area indicates the time of onset and course of a paralytic attack of poliomyelitis; the shaded area indicates the time of onset and course of an abortive attack of poliomyelitis; the open area indicates a minor poorly defined illness. The + and 0 marks are placed at the time the sampling of stool and throat was done.

## T R FAMILY

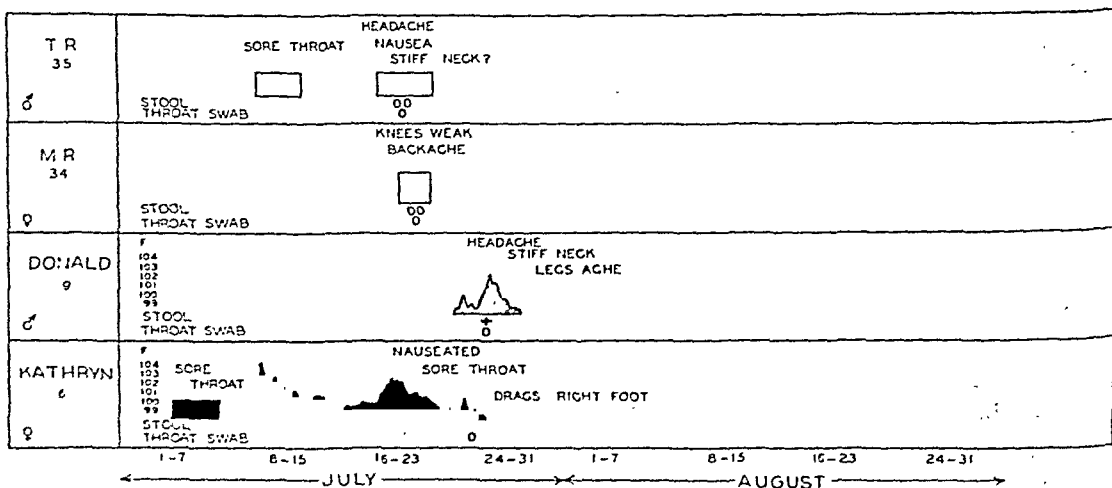


Fig. 5. Schematic diagram of T.R. Family.

The horizontal lines represent different individuals of the family, their ages and sex appear on the left hand side of the figure. The black area indicates the time of onset and course of a paralytic attack of poliomyelitis; the shaded area indicates the time of onset and course of an abortive attack of poliomyelitis; the open area indicates a minor poorly defined illness. The + and 0 marks are placed at the time the sampling of stool and throat was done.

(rural) Paola, Kansas. On July 23, 1946, this family visited a boys' camp where one of the members within the week had been sent to a hospital with poliomyelitis. The family visited a cousin who was in the camp; however, none of the family got out of the automobile. During the last week in July a cat on their farm was sick. The cat had a stiff and staggering gait. The cat died; Mr. C. buried it. About August 5 he complained that his legs were stiff and his arms weak. These symptoms improved slowly during the next 10 days. On August 11 Charles, *aet.* 7 years, had sore throat. His face had a flushed appearance. On August 14 he complained that it hurt him to bend his neck. Following admission to the hospital he developed paralysis of the left arm. There were 1650 cells/mm<sup>3</sup> in the cerebrospinal fluid; 75% of these were lymphocytes. Ann, *aet.* 6 years, became sick on August 13 with fever (103° F.) and sore throat. She was better on the following day, but on August 16 complained of headache. Her neck was stiff. On admission to the hospital she had 1184 cells/mm<sup>3</sup> in the cerebrospinal fluid. Of these 73% were lymphocytes. She developed paralysis of both arms. Mrs. C., *aet.* 34 years did not have a recognized illness.

In summary, the 2 children in this family had paralytic, and Mr. C., father, had abortive poliomyelitis. Poliomyelitis virus was detected in the stool and oropharyngeal samples obtained from each of these 3 individuals. Virus was not detected in similar samplings obtained from Mrs. C.

The onset of illness in the children in the household occurred within a three-day period. It is not at all certain that Mr. C. had poliomyelitis as early as August 5. There is some reason to believe otherwise, for it appears to be the rule that virus is most easily detected

in the oropharynx within the first week of illness. Recent evidence indicates that virus can be detected in the pharynx 1 to 5 days before<sup>3,18</sup> and 1 to 6 days<sup>8</sup> after onset of poliomyelitis. It would appear probable that Mr. C. was seeded with virus at the same time that his children were.

*Family T.R.* (Figure 5.) Residence—Mission, Kansas. Kathryn, *aet.* 6 years, on July 3, 1946 developed sore throat. She had fever (102° F.). During the next 6 days she felt better, but was not completely well. On July 9, she complained again that her throat was sore and again she had fever (104° F.). On July 11 she felt better. On July 14, she had nausea, headache and a stiff neck. On July 17 it was noted that she dragged her right foot. She was admitted to the hospital. The spinal fluid contained 37 white cells/mm<sup>3</sup>; all of these were lymphocytes. The Achilles and patellar reflexes were absent on the right. No further paralysis appeared. On July 10, 1947 Mr. R., *aet.* 35 years, had sore throat. From July 20 to 22 he had headache and backache. He was nauseated, and he had diarrhea. On July 21, Mrs. R., *aet.* 34 years, had a day of backache. On July 24, Donald, *aet.* 9 years, complained that his legs ached. His temperature was 100° F. On July 25, his neck was stiff. He recovered without further progress of his illness.

In summary, in this household 2 children had poliomyelitis. In these siblings onset of illness was at least 15, possibly 24, days apart. Poliomyelitis virus was found in a stool sample obtained from the abortive case. The stool obtained from the paralyzed patient was not tested. The history of minor illness in the parents suggested that they had poliomyelitis but tests for the presence of virus in the throat and

¶ I am indebted to Dr. Paul Loran for the privilege of studying this family.

These data are at variance with those published earlier (Proc. Soc. Exp. Biol. and Med., 66, 92, 1947). It is sometimes difficult to decide whether individuals are apparently healthy carriers; in the final analysis individuals with apparently trivial complaints, namely headache, backache, etc., have been classified as having indefinite illnesses. In the earlier publication some of these individuals were regarded as not having had any illness. We feel that this classification is not important, and that regardless of a negative history the presence of virus indicates a *subclinical level of infection*.



stool (2 monkeys for each stool specimen) were negative.

In this family study there are seen different forces than those seen operating in previous households studied. For example, it is not unlikely that Kathryn had two illnesses, the first, with sore throat, beginning July 3, and the second, poliomyelitis, beginning on July 9. Also, on the basis of the presence or absence of poliomyelitis virus in brother and parents, despite the history of minor illness in the latter, it would appear that the siblings were exposed independently to poliomyelitis virus, and possibly that the parents had no intimate exposure to virus, although exposed to the illness.

*The data assembled here point out that the virus of poliomyelitis is distributed widely in certain households in*

*which the disease appears. The seeding of virus in members residing in 4 households appears to have been simultaneous, and occurred at a common source. In the last, the T. R. family, independent exposures probably occurred.*

*B. Distribution of poliomyelitis virus in throat and feces.*

1. *According to age and illness.* We have summarized in Table 2 some facts concerning the overall distribution of poliomyelitis virus in the throat and feces obtained from individuals in these 5 families. Among 10 adults 7 had some complaint, disregarding the apparently trivial nature of their illnesses. Three of these had virus in their stools and in one, virus was present in the throat sample. The remaining 3 adults were presumably healthy during the

TABLE 2. OVERALL DETECTION OF VIRUS IN THROAT AND FECES ACCORDING TO AGE AND SICKNESS

Group	Age Span (Years)	Number in Group	Sick		Not Sick		Total	
			Virus in Throat	Virus in Feces	Virus in Throat	Virus in Feces	Virus in Throat	Virus in Feces
Adults	28-43 yr.	10	1/6†	3/7	1/3	1/3	2/9†	4/10
Children	7 mo.-11 yr.	14	5/14	13/13*	—	—	5/14	13/13
Total	—	24	6/20	16/20	1/3	1/3	7/23†	17/23*

Numerator=positive tests, denominator=individual tests completed.

\* One stool from a paralytic case (T.R. family, Kathryn *aet.* 7 years) not tested.

† One test was incomplete; See Table 1.

TABLE 3. DETECTION OF VIRUS IN THROAT AND FECES ACCORDING TO TYPE OF ILLNESS AND INTERVAL BETWEEN ONSET AND SAMPLING<sup>5</sup>

Type of Illness	No. of Cases	Mean Interval in Days Between Onset and Sampling		Positive Tests	
		Feces	Oropharynx*	Feces	Oropharynx
Paralytic	7	8.6	6.7 (3.2)	6/6 (7/7)	4/7
Abortive	7	7.4	7.5 (2.0)	7/7	1/7
Indefinite	7	11.2	11.2	3/7	1/6
None	3	—	—	1/3	1/3
Total	24			17/23 (18/24)	7/23†

\* Actually these are approximations since in several instances we have found it difficult to state the exact time of onset.

One stool noted above not tested; (7/7) includes a test presumed to be positive.

† One test was incomplete; see Table 1.

period of study; 1 of these had a sub-clinical attack of poliomyelitis. In this last patient poliomyelitis virus was present in the throat and bowel. Of 14 children, 7 had paralytic, and 7 had abortive attacks of poliomyelitis. Stool samples from 13 children yielded poliomyelitis virus (one stool from a paralyzed patient was not tested); virus was detected in the throat of 5 of these children.

In these households the risk of attack among children is twice that observed to have occurred among adults.

2. *According to type of illness.* The data tabulated in Table 3 indicate that it is easy to detect virus in the throat of the paralyzed patient. Virus was detected in the throat of 4 of 7 paralyzed children. In abortive poliomyelitis virus in the throat has not been as readily detected as in the paralyzed patient. Among 7 abortive cases whose stool samples were positive in only one, a child, was virus detected in the oropharynx. Among those 7 individuals (adults) whose complaints were so poorly defined the classification has been difficult, virus was detected in the stool of 3, and in 1 it was found in the oropharynx. Virus was found in the stool and throat of one apparently healthy adult.

It is evident that poliomyelitis virus disappears from the surface of the throat soon after the onset of poliomyelitis. Two major queries arise from this observation. Is the difference in ability to detect virus in the paralytic and abortive types of poliomyelitis an indication that there is more virus in the throat of the paralyzed patient? Or is the interval between onset of illness and sampling of great importance?

3. *According to interval between onset and sampling.* The number of days between onset of illness and sampling of the exudate in the oropharynx and stool among patients, particularly in

respect to type of illness, appears also in Table 3.

The duration of the fecal carrier state has been studied,<sup>5</sup> and, except to state that virus may be excreted in feces for from 3 to 18 weeks, need concern us no further here.

A somewhat different situation exists in respect to the presence of virus in the throat. It was stated earlier that virus can be detected readily in the early days of illness and even before sickness appears<sup>3</sup> but the ease of detection is reduced markedly after the first week of illness. In the present series there is little observed difference in the mean interval between onset of illness in paralytic and abortive attacks of illness and sampling of the oropharynx for virus. The results of tests however indicate that virus was most easily detected in samples from paralyzed patients.

Actually among the paralyzed cases positive throat swabs were obtained only during the first few days of illness (indicated parenthetically in Table 3); the inclusion of the negative test tends to prolong the mean interval for the group, and obscures the true and approximate interval in which positive tests were observed to occur. In the abortive cases the mean interval represents quite closely the actual time between onset and sampling. The single positive throat in this group (1/7) was obtained on the second day of illness.

It would appear that time is the essence of importance in sampling, and that clinical gravity of illness is of little significance in regard to the presence of poliomyelitis virus in the oropharynx.

*Discussion.* In résumé there are situations favorable to a widespread dispersion of poliomyelitis virus in households in which the disease appears. How virus is seeded in these individuals is not in evidence from our

data. It appears, for reasons stated below, that the seeding and subsequent implantation of virus in people in 4 families occurred at the same time.

It is now clear that poliomyelitis virus can be detected in the throat and in the feces of infected individuals prior to the appearance of symptoms,<sup>3,18</sup> This clarifies certain aspects in pathogenesis, but not in epidemiology. The presence of virus in the throat during the prodromal period requires interpretation. The throat probably provides one of the primary niduses for implantation of virus, thereby providing access to pathways leading to involvement of the central nervous system. Ward and Walters<sup>14</sup> detected virus on a face mask containing materials expelled from the mouth (or nose) in 2 (of 19) patients. Nevertheless it was difficult to find virus in such material albeit these patients were in the first 2 or 3 days of illness. In spite of these findings one cannot be certain yet that the presence of virus in the oropharynx is not of greater pathogenic than epidemiologic interest.

In the present study, it is surprising, due consideration being given to the demonstrated presence of virus in the throats of children, that among intimate attendants, namely their mothers, none had poliomyelitis virus in the oropharynx. Although the series is small, this is not a sampling error as attested to by the negative stool tests in all except one. If these mothers are "immune" to poliomyelitis they stand in distinction to other members of their household.

There remains a possibility in view of the obscure onset and nature of illness that two fathers might have brought poliomyelitis virus into the household. This does not appear tenable because virus is present in the throat probably a few days before and after onset of illness, and virus was detected in the throat of these men at the same time that it was found

in the oropharynx of other members of their families. Hence, it appears that virus was seeded in the fathers simultaneously with other family members.

Primary exposure may also occur independently in siblings living in the same household. This is not a unique observation, for such primary contacts are not uncommonly seen in some diseases of respiratory and alimentary origin. In particular, in the random movements of children between 5 and 10 years, it is not unlikely that they have many opportunities for single or repeated exposure to many microorganisms at least potentially capable of causing illness, and among these is poliomyelitis. In some households there are members who are exposed in an experience in which other members of the family do not share. These individuals introduce virus into the family, and while circumstantial evidence suggests that they may seed it among other residents, it is not clear beyond peradventure that they do.

The validity of using simultaneous appearance of illnesses in members in a group to indicate common exposure to a microorganism is questionable unless the broad limits of the incubation period are known. Horstmann and Paul<sup>4</sup> have discussed this problem. Inasmuch as the mode of spread and the *extra-neural* pathogenesis of poliomyelitis has not been succinctly defined the prodromal period in poliomyelitis is a matter of opinion.

Precisely what the situations are which determine a widespread seeding of poliomyelitis virus in the family are not known. Zintek<sup>18</sup> has suggested a common vehicle rather than a person. To this we agree.

Summary. 1. A study of 5 families in which poliomyelitis appeared provided evidence of a widespread distribution of virus in members of these households.

2. There were 24 members in these

households; 17 had poliomyelitis virus in their intestinal discharges; in 7 virus was detected in the throat.

3. Poliomyelitis virus was detected in stool samples of 13 children, and 4 adults. Virus was present in the throat of each of 5 children and 2 adults.

4. On the basis of history of onset of illness and isolation of poliomyelitis virus in members of 4 households it is suggested that virus was seeded in respective members at a common source.

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# THE MAINTENANCE OF PATIENTS WITH TROPICAL SPRUE BY MEANS OF MASSIVE DOSES OF SYNTHETIC 5-METHYL URACIL (THYMINE)\*†

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It has been amply demonstrated, within the past 2 years, that synthetic 5-methyl uracil (thymine) (Fig. 1) is capable of producing a clinical and hematologic response in the patient who has macrocytic anemia of pernicious anemia, of nutritional deficiency disease, and of tropical sprue. It has been pointed out by Spies and his

is not an effective agent in the prevention of subacute combined degeneration in patients with Addisonian pernicious anemia. They noted also that it is not effective in retarding the progress of subacute combined degeneration once it has been initiated.

The present study, unlike any previously reported, is concerned with the maintenance of 3 selected patients, suffering from tropical sprue in relapse, for at least 1 year after the administration of large doses of thymine.

**Materials and Methods.** Three white Cubans (2 men and 1 woman) were selected for study, using the following criteria:

1. The patient must have a macrocytic anemia with a red cell count of 2.5 million or less per c.mm. and a color index of 1.0 or more.

2. There must be megaloblastic arrest of the sternal bone marrow.

3. The patient must have diarrhea, characterized by voluminous foul-smelling, frothy, liquid, yellow stools, with an increased fat content as determined by

## THYMINE

(2, 4, Dioxo - 5 - methyl pyrimidine)

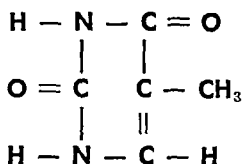


FIGURE 1.

associates<sup>1,3,4,6</sup> that this clinical and hematologic response parallels that which follows the administration of folic acid, provided the dose of thymine is several thousand times that of folic acid. Spies and Stone<sup>5</sup> have noted further that thymine, like folic acid,

\* Northwestern University Studies in Nutrition at the Calixto Garcia Hospital, Havana, Cuba, in cooperation with the University of Havana.

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chemical analysis.

4. He must have glossitis.

5. There must be free hydrochloric acid in the gastric juice on fractional analysis after histamine stimulation.

6. He must have a flat oral glucose tolerance curve as determined by an increase in blood glucose of no more than 10 mg. per 100 cc. in subsequent blood samples compared to the fasting specimen, no sample being greater than 105 mg. per 100 cc.

7. The intestinal pattern on radiography must have a "moulage" appearance and other findings consistent with a diagnosis of sprue.

8. The patient must have had a body weight loss of at least 20 pounds during the 6 month period preceding the initiation of the study.

9. He must have had no specific therapy within the 5 weeks preceding the initiation of this study.

The patients selected were admitted to the Calixto Garcia Hospital. In each case, a complete medical and dietary history was obtained and a complete physical and neurological examination made. Packed cell volumes (P.C.V.) with blood indices were determined prior to and after therapy. Daily erythrocyte, leukocyte, hemoglobin, and reticulocyte determinations were made by methods

previously described.<sup>4</sup> Before therapy was initiated and at the peak of reticulocytosis, sternal bone marrow was obtained by aspiration. Gastrointestinal Roentgen ray examinations were done by Dr. R. L. Hernandez Beguerie before treatment and on the 15th day of therapy. Glucose tolerance tests were done before and after treatment. The stools were examined for parasites by Dr. Arturo Curbelo and cultured for bacteria by Dr. Pedro Kouri. Gastric analyses were done by Dr. Aureliano Rodriguez. The diet of each patient, which was rigidly controlled throughout the time the patient was in the hospital, contained no meat, meat products, fish, fowl, milk or eggs. All other foods were allowed in any amount desired.

After baseline studies were completed, each patient was given a total of 15 grams of synthetic 5-methyl uracil daily in two 7.5 gram doses, one at 10 a.m. and one at 3 p.m. The material was suspended in a half glass of water immediately before administration. The patients remained in the hospital until they had gained weight and strength and until their blood values approached normal. When they were discharged, they were instructed to eat a diet high in calories, protein, minerals, and vitamins and to return at regular intervals for follow-up studies.

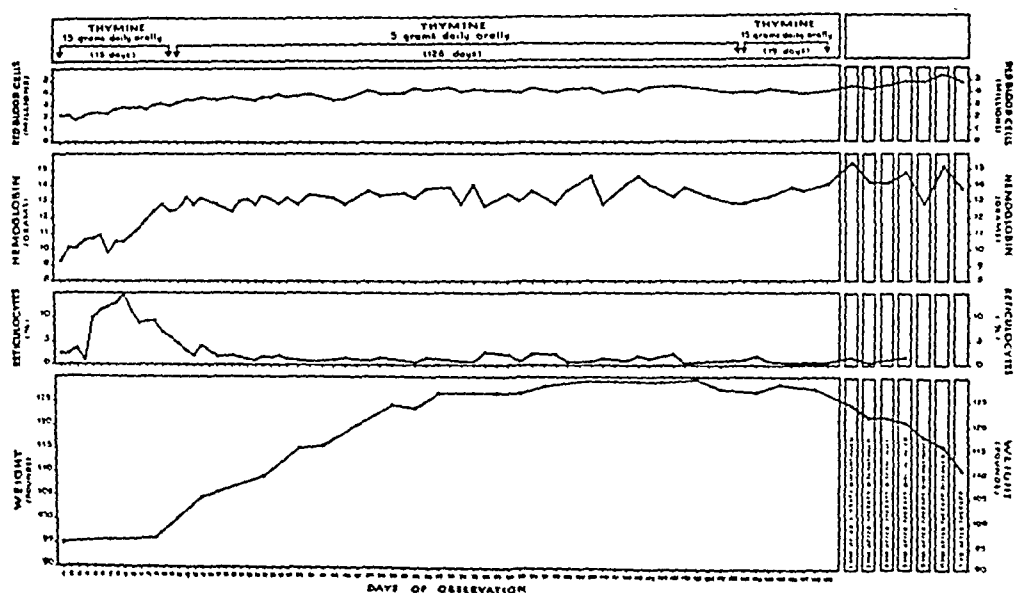


FIG. 2.—Case 1.—Hemopoietic response and weight during thymine therapy and for 1 year thereafter.

**Observations.** Following the administration of 5-methyl uracil, a definite hematologic response took place in each of the 3 patients as can be seen in Figures 2, 3, and 4 and in the summary of cases shown in Table 1. Reticulocytosis, which began on the 4th or 5th day of therapy, reached a peak on the 8th or 9th day and was followed by an increase in erythrocytes and hemoglobin. Examination of the sternal bone marrow obtained on the day after the peak of reticulocytosis showed that in each case the marrow had changed and that it now contained more normoblasts, with al-

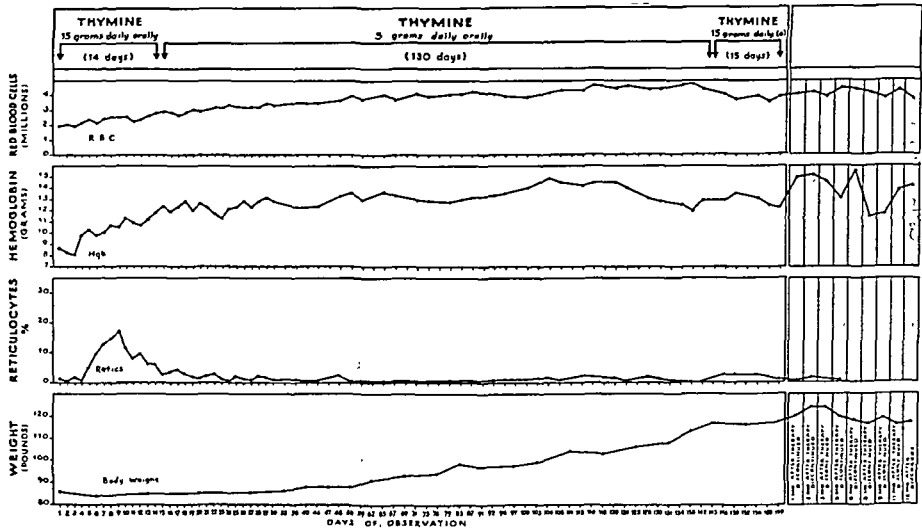


Fig. 3.—Case 2.—Hemopoietic response and weight during thymine therapy and for 1 year thereafter

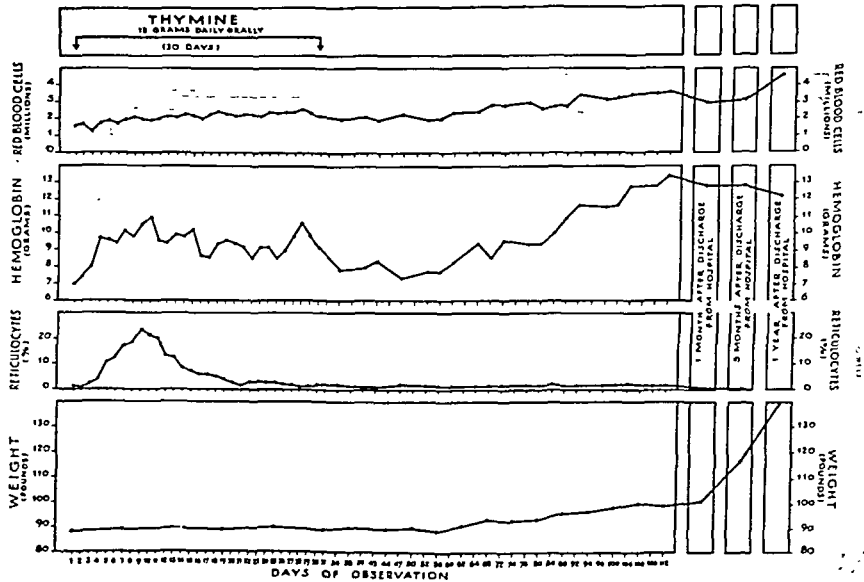


Fig. 4.—Case 3.—Hemopoietic response and weight during thymine therapy and for 1 year thereafter

MAINTENANCE OF PATIENTS WITH TROPICAL SPRUE

TABLE 1. HEMOPOIETIC RESPONSE OF PATIENTS WITH TROPICAL SPRUE TO THYMINE (5-METHYL URACIL): MAINTENANCE OF BLOOD LEVELS AND CLINICAL CONDITIONS 1 YEAR AFTER THERAPY DISCONTINUED

TABLE 1. HEMOPOIETIC RESPONSE OF PATIENTS WITH ANEMIA AND CLINICAL CONDITIONS 1 YEAR AFTER THERAPY															Therapy, Thymine (5-Methyl Uracil)		Remarks
Case No.	Name	Erythrocytes (millions/c.mm.)		Hemoglobin (g./100 c.c.m.)		Leukocytes (per c.mm.)		Reticulocytes (%)		g. per day	Days of Admin- istration						
		Initial	After Therapy (Months)	Initial	After Therapy (Months)	Initial	After Therapy (Months)	Initial	After Therapy (Months)								
1	R.V.	2.19	3.95 (160)	4.81 (12)	9.3	14.0 (160)	13.8 (12)	7,300	7,100 (160)	7,150 (12)	2.4	9	14.8	0.4 (12)	15	14	Works daily as a fireman in a steel plant. Feels strong. No recurrence of anorexia, soreness of the mouth or tongue, epigastric distress, abdominal distention or diarrhea. Has one normal stool daily. Appetite good. Diet good except for green vegetables. Gained 41 pounds following therapy. Three months ago had severe cold, lost appetite, heavy work required more energy than decreased intake supplied. Lost weight which he has not regained.
2	A.H.	1.97	3.89 (159)	3.07 (12)	8.7	12.4 (150)	14.2 (12)	7,700	11,800 (159)	7,900 (12)	1.2	9	17.0	0.6 (12)	15	14	Working regularly as night watchman. Strength good. No recurrence of anorexia, soreness of mouth or tongue, epigastric distress, paresthesias of hands or legs or diarrhea. Has one normal stool daily. Appetite good. Diet better than before therapy but includes insufficient amounts of animal protein and green vegetables. Has retained the 30 pounds of weight gained following therapy.
3	J.B.	1.58	3.66 (112)	4.57 (12)	7.0	13.4 (112)	12.2 (12)	4,450	9,300 (112)	4,200 (12)	1.0	9	23.6	1.4 (12)	15	14	Feels well. Strength good. Does all housework for herself and family of 5. No recurrence of anorexia, soreness of mouth or tongue or diarrhea. Has 1 normal stool daily. Appetite good. Diet excellent. Has gained 41 pounds since treatment.



most complete obliteration of the megakaryoblastic arrest seen in the preparation obtained before therapy was initiated. Clinical improvement began at approximately the same time as reticulocytosis. The patients stated that they felt stronger and their appetites returned. The glossitis and burning and soreness of the tongue disappeared, and the stools returned toward normal although they did not become completely normal for six weeks. Gastrointestinal Roentgen ray findings following therapy were similar to those already reported from this clinic.<sup>2</sup> Each of the patients gained weight in the hospital and was free of symptoms at the time of discharge.

During the year which has elapsed since these patients were given massive doses of 5-methyl uracil, their blood values have been maintained at normal levels. They appear to be in excellent health and are working hard every day. They have had no recurrence of diarrhea or other alimentary tract symptoms. The authors have observed a few patients with tropical sprue, however, whose alimentary tract symptoms did not disappear completely on thymine, folic acid or liver extract therapy.

**Summary and Conclusions.** 1. The present study shows that massive doses of synthetic 5-methyl uracil (thymine) are effective in inducing a hematologic and clinical response in persons with tropical sprue in relapse.

2. For the first time it is reported that the blood values and general health of patients with tropical sprue in relapse were maintained for at least a year after the administration of large doses of synthetic thymine.

3. In these patients with tropical sprue there was no evidence of subacute combined degeneration at any time during the course of the study. In our studies of patients with Addisonian pernicious anemia in the United States, we have learned that thymine, like folic acid, neither prevents the development of subacute combined degeneration in these patients nor does it retard it once it is initiated.

4. The authors do not recommend thymine as a practical therapeutic agent as it has no virtues over folic acid which have been demonstrated so far, and it takes several thousand times the dosage to produce a response equal to that which follows the administration of folic acid.

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# THE HEALING OF RESISTANT SKIN ULCERS AFTER TREATMENT WITH NITROGEN MUSTARD

A PRELIMINARY NOTE

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In the course of an investigation on the therapeutic value of nitrogen mustard, it was observed that skin ulcerations, resistant to all previous forms of treatment, started to heal. These properties of nitrogen mustard to our knowledge have not been heretofore described in the literature.

This observation was accidentally made while using nitrogen mustard for a neoplasm of the spine on a 23 year old patient suffering also from a large decubitus. Although the nitrogen mustard treatment had no therapeutic effect

on the neoplasm, the ulcer was covered in 5 to 10 days with epithelium and the pain had decreased.

Another case was a patient, 42 years old, who had undergone an operation for carcinoma of the penis followed by irradiation with large doses of x-ray in the inguinal region. After the last series of irradiation in February 1947, an ulceration appeared in the right groin and in spite of various forms of treatment, it continued to spread and deepen. He was admitted to the clinic in September 1947 with a wide-



Fig. 1.—Ulceration in the right inguinal region caused by irradiation with large doses of x-rays (carcinoma penis). Before treatment with nitrogen mustard.

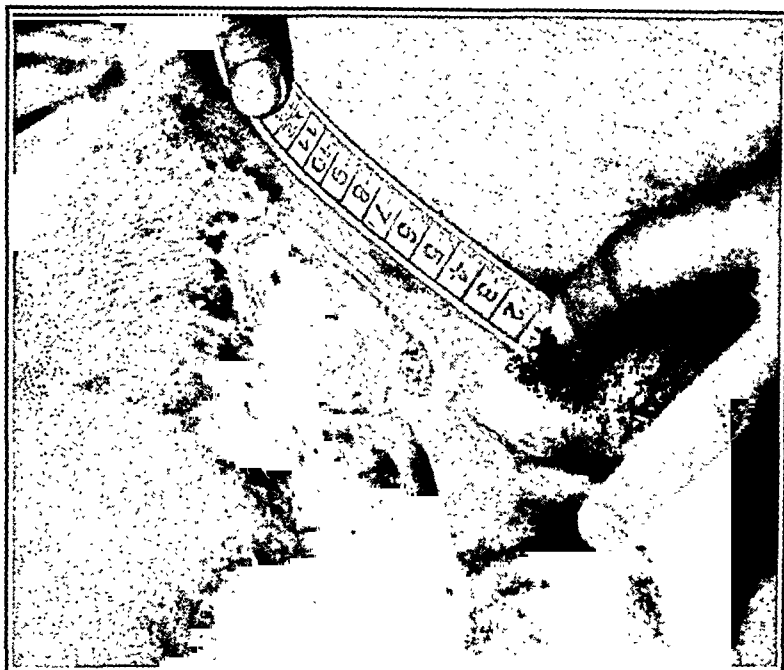


Fig. 2.—Same ulcer 2 months later after treatment with nitrogen mustard.



Fig. 3.—Same ulcer after 18 weeks.

spread deep wound affecting three-fourths of the right groin (Fig. 1). Nitrogen mustard treatment was instituted after determining his sensitivity by the aid of the skin test<sup>1</sup> developed in our laboratory.

The test is performed as follows. After removing all traces of fat from the skin of the forearm, one drop each of 1%, 0.1% and 0.01% alcoholic solution of nitrogen mustard is applied to the surface of the skin and the changes are observed after 24 and 48 hours. The skin to which the solution has been applied becomes red in most cases after 24 hours. When the reddening appears in the place where 1% solution has been applied, the reaction is regarded as positive (+); when reddening appears with 0.1% solution it is a strong positive reaction (++); and with 0.01% solution it is a very strong positive reaction (+++). In very strong positive reactions a wheal may appear.

In our experience these skin tests have proved of value in determining the dosage of nitrogen mustard. In the majority of cases we have observed that the systemic toxic symptoms run parallel to the skin tests. Our patients with a +++ reaction tolerated only 0.025 mg. per Kg. of nitrogen mustard. Patients with a ++ reaction tolerated

0.05 mg. per Kg. and patients with a + reaction tolerated 0.1 mg. per Kg.

After the patient received 6 mg. of the drug intravenously daily for 6 days the pain disappeared, the floor of the ulceration was covered with granulation tissue and the edges showed a marked tendency to contract. He then received, at 2 six-week intervals, series of nitrogen mustard consisting of 3 and 2 intravenous injections respectively of 6 mg. each. The wound continued to decrease in size, the granulation extended to the surface of the skin and was covered with epithelium. By the middle of November the area of the ulcer was much smaller, the floor had risen to the level of the skin and was partially epithelialized (Figs. 2 and 3).

We have made similar observations in other cases and found that nitrogen mustard affects superficial decubitus as well as deep skin ulcerations resulting from x-ray burns, which as we know are among the most difficult of skin wounds to heal.

These observations are submitted as a preliminary report. Further investigations are being carried out in our clinic on the response of other non-malignant types of lesions of internal organs to nitrogen mustard.

<sup>1</sup> J. Aleksandrowicz and A. Wolanski, to be published.

# THERAPY OF ACUTE FLUORIDE POISONING

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THE literature dealing with the biological effects of fluorine and fluorides has grown rapidly in the last three decades. The principal incentive for this was the discovery in 1931 that naturally occurring fluorides could and did affect dentition<sup>38</sup>. The many and ubiquitous uses of fluorine compounds in agriculture and industry have also inspired much investigation of the toxicity of fluorides.

In the interests of clarity, fluorosis may categorically be divided into 3 types: (a.) Chronic, low-dose poisoning, giving rise to dental defects and perhaps to other less well understood phenomena. This type of poisoning is not known to cause physical incapacitation, and is primarily the result of ingestion of excessive amounts of naturally-occurring fluorides in drinking water supplies. (b.) Chronic, high-dose poisoning, resulting in bone disease (Roholm's "cryolite fluorosis"<sup>48</sup>) and other afflictions which may seriously affect the victim's subjective well-being<sup>3,37</sup>. This type is usually associated with industrial exposure of workers, or of the inhabitants of industrial regions.<sup>40</sup> (c.) Acute fluoride intoxication due to ingestion or inhalation of relatively large amounts of fluorine in elemental form or in chemical compounds.

The third form, acute fluoride intoxication, be it accidental, suicidal or homicidal, has not been examined with the same vigor that has characterized the investigation of the other two. Reviews of fluorine physiology and tox-

icity<sup>10,19,35</sup> have tended to minimize the significance of acute effects. Quantitative or metabolic studies of this condition have been few, and the important implications of some of the available data have not been appreciated. It has therefore seemed advisable to employ a case report as the framework for a discussion of certain pertinent aspects of the acute type of fluorine poisoning.

**CASE REPORT.** F.B.M., No. A57262, a 16-year-old, white, unmarried, schoolgirl-store-clerk, was brought to the emergency room of the New Haven Hospital on October 8, 1946, at 9:45 a. m. Her uncle, who brought her to the hospital in his car, stated that she had awakened him 20 minutes earlier to inform him that she had just taken poison following an argument with her mother. She had also complained of severe stomach pain. The patient admitted to taking one-third or one-half of a drinking glass of roach powder mixed with water.

*Previous history* included several visits to the hospital's clinics for minor complaints. She had had no known serious illness or injury. The family was broken, and social and legal agencies had been repeatedly called on because of poverty and a sibling's moral offenses.

*Admission examination:* T99.6 P 80 R 16. B.P. 120/80. The patient was a well-developed and nourished, acutely ill, white, adolescent female, appearing somewhat older than her stated age. Positive findings follow. She lay motionless on a stretcher, responding dully and reluctantly to questions and asking that she be allowed to die. At intervals she was racked by abdominal cramps which caused her to writhe and cry out in pain; these were usually followed by emission of cloudy opalescent, bright green vomitus and involuntary watery diarrhea. The skin was dirty and pale

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with marked erythema and slight induration at sites of contact with vomitus on face, neck and chest.

The mucous membranes were quite pale. There was periodic emission of a watery mucinous discharge from the nares mixed with vomitus. Salivation was profuse and watery. The pharynx was injected. The thyroid was easily palpable and diffusely enlarged. Respiratory motions were slow and shallow. Large, mature, tense breasts showed easily visible periareolar venous nets. The lung fields were clear except for loud, coarse tracheal ronchi. Aside from tachycardia, precordial signs were not revealing. A tense, scaphoid abdomen emitting grossly audible peristaltic rushes at 1 to 5 minute intervals was tender throughout, even to light touch.

*Course and treatment:* The immediate impression of the emergency room staff was that the poison had been arsenic. The stomach was washed and magnesium sulfate administered by tube. The author saw the patient 30 minutes after admission, and in the interim the pulse had risen to 100, respirations had fallen to 12, and the blood pressure was only 100/70. Intravenous injection of 1,000 cc. of a 5% solution of glucose in distilled water was started, and the girl's uncle was dispatched for the poison container. Since the blood pressure continued to fall, 500 cc. of pooled plasma were started at 11:30 a. m. Shortly thereafter the poison can was produced, and it was found that the substance had been sodium fluoride roach powder, a legally-required pigment accounting for the bright green color of the vomitus.

Lime water (0.15%  $\text{Ca}(\text{OH})_2$ ) was immediately obtained and 4 ounces administered by mouth, followed by 1 ounce every 30 minutes for the next 12 hours. A continuous intravenous infusion of alternating glucose solution and of normal saline (plus 1 pint of whole blood) was maintained during the first 24 hours to combat enteric fluid loss and shock. This included 2,500 cc. of 10% glucose and 1,000 cc. of normal saline, making a total parenteral fluid intake of 5,500 cc. During the first 2 hours of treatment the patient improved noticeably, although the temperature rose to 102 and acute discomfort continued. Digifoline (8 cat units) was administered intravenously to facilitate full digitalization should indications appear, but none developed.

Calcium gluconate was kept in a syringe at the bedside, and when some 4½ hours after admission, the patient developed positive Chvostek and Trousseau signs and com-

plained of numbness and tingling of the extremities, two ampules were administered intravenously with prompt relief. Additional calcium gluconate was administered in the continuous infusion during the first night. Later in the afternoon the patient vomited up bright red specks of tissue, one or two of which measured as much as 1 by ½ by ¼ cm. On microscopic examination these proved to be plates of mucosal epithelium, presumably gastric. Examination of a blood sample for hemolysis at this time was negative. The local erythema of face and chest ("vomitus burns") was still noticeable 7 hours after admission.

The next morning, 24 hours after poisoning, the patient was dramatically improved. Although complaints of aching and tingling of the arms suggested recurrence of tetany, absence of other signs caused this to be ascribed to frequent venepunctures and to the intravenous infusions. A subsequent determination of serum calcium confirmed this (Table 1). A liquid diet was given, and on the 3rd hospital day a full diet was resumed. Temperature returned to normal 48 hours after admission, and on October 11 the patient was sitting up in a chair virtually recovered.

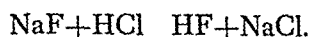
An Ascheim-Zondek test on October 14 was positive. The patient then admitted that she had taken the poison to avoid the decision that had greeted two neighborhood girls who had borne children out of wedlock. After 7 days in the hospital she was discharged to court custody in accordance with law. Some weeks later she was married.

The patient was followed in prenatal clinic, although irregularly because of her recalcitrance. Gestation was uneventful except for mild anemia and an isolated instance of glycosuria (1+) which was not subsequently confirmed. On May 26, 1947, she bore a normal son at term, and post-partum examination in July, 1947, revealed no abnormalities.

Pertinent laboratory data include: on October 8, 1946, 14,000 leukocytes (16% non-segmented, 62% segmented neutrophils, 18% lymphocytes and 4% monocytes); on October 16 the count was 6,800 (4% non-segmented, 65% segmented neutrophils, 21% lymphocytes, 6% monocytes and 4% eosinophils). On 5 occasions the urine was negative, except for glycosuria during glucose infusions. Roentgenograms of chest and long bones were negative, but some teeth were found carious and abscessed. On October 11, the electrocardiogram was found, "probably normal, with borderline large  $Q_3$ ." On October 15 the

prothrombin time was normal and the stool negative for blood. Chemical data are summarized in Table 1.

**Discussion.—CHEMISTRY.** The phenomena observable when the human or animal is exposed to fluorine gas or to chemicals containing fluorine are in part directly ascribable to known chemical and physical properties of these compounds. Fluorine is well characterized as one of the most "active" of the elements. Of a total of 208 compounds containing fluorine listed in standard tables of inorganic chemicals<sup>23,29</sup> 55, or over 25%, decompose in water, and information is lacking for 20 others. Elemental fluorine and its acid, HF, are well known



It is probably justifiable to assume that the intense intestinal activity with cramps, borborygmus, vomiting and diarrhea, all common symptoms of acute poisoning seen in this patient and repeated in others, are the result of this corrosive effect. It is also likely that the renal irritation<sup>14,16,44</sup> and the kidney damage noted at autopsies are attributable to the same mechanism, accentuated by concentration of the fluorine compounds by the excretory mechanism<sup>14,16,49</sup>.

A less immediate but equally important effect of large doses of fluoride, once it has entered the circulation, is its combination with calcium to form

TABLE 1. BLOOD ANALYSES IN PATIENT F.B.M.

Date		Blood		Co. Content meq.	Cl. meq.	Serum		mg. per liter	
		Sugar mg. per 100 cc.	NPN			Protein gm. per 100 cc.	Albumin	Calcium*	Phosphorus
10/8/46	12N	397							
10/9/46		240	20	25	99	5.70	3.75	9.16	1.87
10/11/46		75							
10/12/46		81†							
10/14/46		70	25			6.85	4.90	11.70	3.61

Note: Significance of blood sugars of 10/8 and 10/9 not clear because of glucose infusions. See text.

\* Serum calcium concentration not determined prior to treatment with calcium salts.

† 120 minutes after 25 gm. of glucose, 74 mg.

for their corrosive properties. On the other hand certain fluorine salts, such as  $\text{CaF}_2$  and  $\text{MgF}_2$  are quite insoluble, and many of them are widely distributed in rocks and soils.<sup>19</sup>

The simplest effect of fluorine on the animal organism is a corrosive one, seen on skin contact, inhalation or ingestion of volatile or soluble fluorine compounds. This effect consists of superficial or deep erosive burns of skin or of respiratory or digestive mucosa.<sup>15,16</sup> In the case of F.B.M., this effect was apparent both on the skin areas in contact with vomitus and later from the vomiting of digestive tract epithelium. A specimen of the vomitus, sealed and stored in the refrigerator for medico-legal purposes, was subsequently found to have etched the glass vial in which it was placed. Presumably the reaction with gastric contents proceeds as follows:

the insoluble salt  $\text{CaF}_2$ . This effect in the test tube has been utilized for the prevention of clotting of blood. In the intact animal or in humans the effect on clotting apparently is not an important factor in the outcome of acute poisoning<sup>20</sup>, although a relationship between coagulation time and chronic, low-dose fluorosis has been recorded<sup>53</sup>. One group reports that coagulation of the blood is actually increased in fatal human poisoning.<sup>16</sup> This observation may represent increased viscosity secondary to shock rather than a specific fluoride effect. The author and his associates have noted a similar phenomenon in rats<sup>9</sup>. It seems most probable that hemorrhagic phenomena noted by many observers in intestinal mucosa at autopsy are secondary to local corrosive action rather than to any generalized vascular reaction or clotting disturbance. A pro-

thrombin time determination on F.B.M. was normal. No bleeding tendencies were noted. A coagulation time was technically unsatisfactory and is not reported.

The most dangerous clinical result of this biological inactivation of calcium is tetany which may, and frequently has, ended in death<sup>34,36,45</sup>, although the tetanic nature of agonal motor disturbances have not always been recognized.<sup>36</sup> It seems probable that many of the "convulsive" phenomena reported in fatal fluorosis were unrecognized tetanic states. The appearance of tetany is usually delayed for 3 to 6 hours after ingestion<sup>45</sup>. Oral and parenteral calcium are therefore important adjuncts to therapy, the former to intercept unabsorbed fluoride, the latter to replace precipitated serum calcium. The efficacy of such therapy was demonstrated in the case of F.B.M. whose clinical tetany, appearing after a typical time interval, disappeared promptly on administration of calcium gluconate. Unfortunately it was not possible to obtain a serum calcium level until 24 hours after therapy. Others have demonstrated similar improvement in the treatment of human cases<sup>49</sup> and in animals<sup>31,43,47,50</sup>, (although no effects are demonstrable with small doses<sup>20</sup>). The time interval between fluoride exposure and the onset of tetany is so short that it is improbable that one is dealing with gastric tetany. Nevertheless chloride loss from emesis undoubtedly contributes in part to the depletion of ionized serum calcium.

The author and his associates<sup>43</sup> have found that calcium and magnesium salts exert a definite protective action in rats given sodium fluoride by gavage. Preliminary experimental data indicate that magnesium does not potentiate fluorine toxicity under our experimental conditions. Of 151 young rats given 0.5 gm. of sodium fluoride,

25 (83%) died within 48 hours. When 40 rats were given 0.12 gm. of calcium chloride, followed by 0.05 gm. of sodium fluoride, only 2 (5%) died in the first 2 days. When the calcium chloride was given 5 minutes after the fluoride (20 rats) the mortality was 10%, and when the interval was increased to 10 minutes (46 rats) mortality rose to 63%. A dose of 0.12 gm. magnesium sulfate in place of calcium chloride gave comparable results. When calcium fluoride alone was given (0.05 gm.) to 35 rats, the mortality remained low, 3 out of 35 rats dying in the 48 hour period (9%). Mortalities at 24 and at 72 hours showed no significant deviations from these figures. This appears to contradict previous evidence obtained by Ranganathan<sup>46</sup> who used lower dosage over a longer period and found that magnesium fluoride was, if anything, more toxic than the sodium salt, causing him to conclude that fluoride toxicity was not a simple function of salt solubilities. Studies by others of the effects of several relatively insoluble fluorides have confirmed a direct relationship between solubility and biological effect.<sup>26,30</sup>

Recently it has been suggested<sup>7</sup> that glycolysis in defibrinated blood may be obliterated by a similar mechanism, namely the formation of the highly insoluble fluorides of magnesium and calcium, thus removing an ion or ions which conceivably participate in this type of glucose catabolism. Fluoride blockage of glycolysis had long been recognized,<sup>6,11,21</sup> and has been a valuable tool in the study of cellular metabolism, but the mechanism of the blockage is as yet incompletely understood.

It is not possible to predict the clinical resultant of the effects of fluoride on carbohydrate metabolism. Data in humans are virtually non-existent. Handler has produced hyperglycemia in rabbits which is counteracted by insu-



lin<sup>21</sup>, and later he and his associates obtained similar findings in rats.<sup>22</sup> In the case presented here (Table 1) the blood sugar was elevated on 2 occasions and glycosuria was noted. Unfortunately interpretation of results is complicated by the fact that the patient was receiving glucose by vein. The subsequent glucose tolerance test indicates that any carbohydrate disturbances which may have occurred were, for clinical purposes, completely reversible. There seems to be no evidence that chronic fluorosis causes glycosuria, despite prolonged absorption and storage of appreciable amounts of fluoride.<sup>3,48</sup> It has been noted that the fasting state predisposes to hypoglycemia rather than hyperglycemia after fluoride<sup>6,25</sup>. This has been interpreted as an indication of inactivation of liver phosphatase.<sup>25</sup> Insulin seems to protect the liver glycogen to some extent<sup>22</sup>. Although the use of insulin was discussed in planning therapy for F.B.M., the absence of definite evidence of serious disruption of carbohydrate metabolism or of acid base balance made it unnecessary.

Fluorides inactivate numerous other enzymes or enzyme systems in the body<sup>11,32,54</sup>, and it seems obvious that many of the seemingly paradoxical phenomena observed are the resultants of several simultaneous interruptions of normal mechanisms. It will be noted above that F.B.M. was given a digitalis compound prophylactically. This was in accordance with instructions on the label of the box of roach powder from which she obtained her poison. Subsequent study of the literature has failed to reveal convincing evidence that any cardiac disturbances which may occur are at all distinct from those to be expected with shock and circulatory collapse.

In the test tube sodium fluoride may cause hemolysis if concentrations rise too high.<sup>8</sup> This phenomenon has

not been observed in intact animals or in human cases, nor was it present in F.B.M. Blood fluoride levels high enough to cause hemolysis are probably not compatible with life.

SHOCK, although a common accompaniment of all corrosive poisons, has received too little attention in discussion of fluoride damage. The effects of ingested fluoride on the digestive tract are prompt, dramatic and dangerous. In a short interval large amounts of fluid may be lost through violent emesis and diarrhea. By conservative estimate of gross measurements F.B.M.'s fluid loss in the first two hours was 1,500 cc. passed by emesis and per rectum. This fails to include profuse salivation and perspiration. The abdominal pain experienced by fluoride-poisoned individuals is also a contributory factor in producing shock. As noted above there seems to be no available evidence that fluorine compounds have a specific effect on the heart or peripheral vasculature, but their general tissue-toxicity effects probably contribute to circulatory inefficiency. A dangerous sequella of peripheral circulatory failure is oliguria, causing increased fluoride concentration in urine and thus potentiating urinary tract irritation and damage. F.B.M.'s urine volume was well maintained throughout, and no evidences of renal irritation were noted.

The occurrence of pregnancy was a provocative element in this case. Transfer of fluoride through the placental barrier to unborn rats has been demonstrated.<sup>39</sup> Fetal death or damage seemed a likely possibility with such intense, though transitory, exposure. Actually the child was grossly normal in all respects. Whether or not its subsequent development will reveal stigmata of the toxic exposure remains to be seen.

OCURRENCE. Reported cases of fluoride poisoning are predominantly

accidental in origin. Crystalline or powdered sodium fluoride, the commonest offender, resembles many common kitchen comestibles, and it has been mistaken for baking soda<sup>4,13</sup>, Epsom salts<sup>12,49</sup>, baking powder<sup>1,28,49</sup>, powdered milk<sup>33</sup>, Rochelle salts<sup>1,49</sup>, starch<sup>36</sup> and laxative salts<sup>36</sup>.

Suicides have been reported but are not common<sup>4,16,18,27,36,45,55</sup>. It is interesting in this regard to note that standard criminological works ignore fluorine poisoning entirely<sup>51,52</sup>. Only 2 recorded instances of the use of fluoride with malice aforethought have been found, one in which an institutional helper tried to discredit a cook by a mass poisoning<sup>24</sup> and one where a man poisoned two elderly females<sup>27</sup>. That such a lethal poison has been neglected by the murderer is doubtless due to its relatively recent appearance\* and to widespread popular acquaintance with less effective agents.

THE LETHAL DOSE of fluoride in humans is not easily determined. As Gettler<sup>14</sup> has pointed out, the dose taken is often unknown and the amount rejected in vomitus (or diarrhea) may be large. The statement<sup>14</sup> that the aliquot unabsorbed but remaining in the intestines is not contributory to fatality is open to question in view of the intense local irritant action discussed above. Several instances of deaths resulting from the swallowing of 4 to 5 gm. of sodium fluoride are available<sup>10,12,16,36</sup>, and from this it is inferred that the average adult, if untreated, will succumb to this dosage. F.B.M. swallowed about 4 ounces of a thicker-than-cream suspension of 95% sodium fluoride in water (estimated to have been 50 to 80 gm.), the largest dosage from which a human has been known to recover. Undoubtedly early vomiting ejected much of this.

THERAPY. The theoretical considerations noted above offer a basis for

logical therapy which is of utmost importance in prognosis. The need to identify the nature of an offending poison should always be obvious. In fluoride poisoning this need is accentuated by the high toxicity of fluorides and by the availability of specific therapy. Tragedies have occurred which might have been prevented had it been possible to identify the offending agent<sup>4,13</sup>.

The physician who identifies the toxic agent as fluoride must still cope with the problem of therapy. Toxicologists stress postmortem findings, lethal doses and to a lesser extent clinical phenomena, but are not usually concerned with therapy<sup>14,15,16</sup>. In 1945, Rabinowitz<sup>45</sup> in a valuable discussion analyzed the information in standard toxicology and pharmacology texts and found it sadly wanting. The author in an emergency trip to the library for information found in Rabinowitz's paper the clue to the therapeutic program employed for F.B.M. One clinical author realized the importance of calcium therapy 10 years earlier<sup>34</sup>. An outstanding therapeutic text mentions oral calcium but not intravenous use<sup>17</sup>. Textbooks of medicine<sup>5,41</sup> are similarly lacking in pertinent information. One pediatrics text notes the tetanic effect of fluoride and the necessity for parenteral as well as for oral calcium<sup>42</sup>. Thus the clinician in an emergency had only one easily-available source of sound therapeutic advice<sup>42</sup> and that an extremely short note. The following general outline of therapy is therefore offered as one which would seem to be the most rational and specific life-saving program in the light of current knowledge of fluoride metabolism.

1. Act quickly. Fluoride may kill in a few minutes, and 3 to 4 hours after ingestion is the most frequent reported lethal interval.

2. Start intravenous therapy with

\* The first recorded case of fluoride poisoning dates from 1899.<sup>1</sup> The homicidal use of arsenic and mercury, of course, has been common knowledge for at least five and a half centuries.

glucose in normal saline promptly, both to maintain blood sugar in case of hepatic glycogen depletion, and to have a venous channel available for transfusion. Shock may kill despite calcium<sup>55</sup>.

3. Wash the stomach gently with saline, or preferably with lime water, and then give lime water at frequent intervals.

4. Have calcium available for intravenous administration and watch closely for signs of tetany. Tetanic death is often rapid.

5. Maintain high urine volume with parenteral fluid.

6. Wash away vomitus, feces and urine promptly to prevent external burns.

**Summary and Conclusions.** There is presented a case of serious acute fluoride poisoning as an illustration of the disturbances of metabolism which may accompany such poisoning, with suggestions as to the principles of therapy supported by experimental data and practical experience.

The wartime introduction of a powerful fluorine-containing rodenticide, sodium monofluoroacetate, which has since been widely used in civilian extermination, presents a serious potential human hazard. No information regarding the effectiveness of the type of therapeutic program given above has been found, but theoretical consideration would seem to justify its trial in the absence of more specific recommendations.

That such a regimen, coupled with careful observation of clinical progress, can be of material value, seems demonstrated by the recovery of a patient who had taken at least 10 times the reported lethal dosage.

"Since the submission of this article for publication the author's attention has been drawn to the article by Flack and Scofield, who report that local infiltration of fluoride burns with calcium gluconate followed by soaking with Epsom salts is effective in the treatment of hydrofluoric acid burns, usually difficult lesions to heal (*Indust. Med.*, 16, 17, 1947.) The success of this method probably also depends on the chemical inactivation of fluoride by calcium and magnesium ions."

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# ONE HUNDRED CASES OF MILIARY AND MENINGEAL TUBERCULOSIS TREATED WITH STREPTOMYCIN\*

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In the 13 months subsequent to April, 1946, therapy with streptomycin was started in 100 cases of acute disseminated miliary tuberculosis and tuberculous meningitis in 47 Veterans Administration hospitals and in 5 civilian hospitals which were under contract with the Administration. The results of treatment in these cases are the subject of the present report. No case has been excluded from the series which has survived more than 24 hours following the initiation of therapy and in which bacteriological proof of the diagnosis was established. Thirty-nine of the 40 survivors were followed until October, 1947.

The arrangements for this study were not difficult. Veterans Administration hospitals were informed that a supply of streptomycin could be obtained for the treatment of miliary and meningeal tuberculosis by a telegraphic request to the Central Office Streptomycin Committee. A presumptive diagnosis was accepted as a basis for initiating and for continuing therapy, although cases in which it was not subsequently established were excluded from the present series. Progress re-

ports were submitted to the Streptomycin Committee by the hospitals at fortnightly intervals during treatment and after its conclusion. It is from these reports and from subsequent correspondence that the present paper has been compiled.

No dosage regimen was prescribed for the treatment of these cases for the good reason that the Streptomycin Committee had no experience on which to base a prescription. The daily intramuscular injection of 1.8 gm., and the daily intrathecal injection of 0.1 gm., was suggested, but the decision in this matter was left to the individual investigator. This has had the happy result of permitting a number of regimens to be explored, although the variations are not as wide, perhaps, as one could have wished. Nor were the rather formidable battery of laboratory tests required of the investigators which were prescribed in the treatment of other forms of tuberculosis; this, because the hazards of the disease so outweighed those of the drug that it was felt proper to treat cases in all hospitals, even in those with momentarily inadequate laboratories.

\* The data composing this paper derive entirely from case reports contributed generously and with care by 87 physicians from the following 47 Veterans Administration Hospitals: Bronx, N.Y.; Columbia, S.C.; Louisville, Ky.; Minneapolis, Minn.; Oteen, N.C.; Kecoughton, Va.; Van Nuys, Cal.; Aspinwall, Pa.; Excelsior Springs, Mo.; Richmond, Va.; Tucson, Ariz.; Whipple, Ariz.; Bay Pines, Fla.; Castle Point, N.Y.; Cleveland, Ohio; Dayton, Ohio; Hine, Ill.; Indianapolis, Ind.; Lake City, Fla.; Los Angeles, Cal.; McKinney, Texas; Nashville, Tenn.; San Fernando, Cal.; Walla Walla, Wash.; Alexandria, La.; Batavia, N.Y.; Danville, Ill.; Dearborn, Mich.; Fargo, N. Dak.; Fort Bayard, N. Mex.; Livermore, Cal.; Martinsburg, W. Va.; Mountain Home, Tenn.; Newington, Conn.; Outwood, Ky.; Rutland Heights, Mass.; Sampson, N.Y.; Topeka, Kan.; Sunmount, N.Y.; Vancouver, Wash.; Wadsworth, Kansas; Washington, D.C.; Waukesha, Wis.; West Roxbury, Mass.; Wichita, Kan.; Wood, Wis.; Phoenixville, Pa.

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**Clinical Material.** All 100 patients were adult males (Table 1); 66 were white, 32 colored, and 2 Indian. Their ages ranged from 17 to 64 years. Fifty-three were under 30 years of age, 26 were between 30 and 39, and 21 were 40 or more.

A pre-existing focus of proven tuberculous infection, which presumably served as the source of the hematogenous dissemination, was present in 92 cases (Table 2) either in the lung, genito-urinary tract, lymph node, or bone and joint. In the remaining 8 cases no such focus was recognized.

All individuals classified as having miliary disease had the acute generalized

disseminated form, characterized by dense seeding on the chest roentgenogram, by fever, severe toxemia, and usually by leukocytosis. The diagnosis was established by the identification of acid-fast bacilli either in the sputum during life or at autopsy. All patients were seriously ill at the time streptomycin was started and their clinical condition was deteriorating. Individuals with the chronic type of miliary disease (that is, protracted hematogenous tuberculosis, characterized by a prolonged illness, vague symptoms, pulmonary densities of variable size, and minimal fever) have been excluded from this report. All cases of meningitis had abnormal spinal fluid findings, including

TABLE 1

Miliary and Meningeal Tuberculosis Treated with Streptomycin: Age and Race

TYPE OF DISEASE	TOTAL NUMBER	AGE IN YEARS						RACE					
		17 to 29		30 to 39		40 & over		White		Colored		Indian	
		Living	Dead	Living	Dead	Living	Dead	Living	Dead	Living	Dead	Living	Dead
ACUTE MILIARY	22	9	3	2	2	5	1	11	4	5	2	0	0
MILIARY FOLLOWED BY MENINGITIS	10	1	4	2	2	0	1	3	4	0	3	0	0
COMBINED MILIARY & MENINGITIS	25	3	11	2	4	0	5	3	11	2	9	0	0
MENINGITIS	43	11	11	5	7	0	9	11	19	4	7	1	1
TOTAL	100	24	29	11	15	5	16	28	38	11	21	1	1

TABLE 2

Miliary and Meningeal Tuberculosis Treated with Streptomycin:  
Pre-Existing Active Tuberculous Foci

TYPE OF DISEASE	NUMBER OF PATIENTS	UNRECOGNIZED		LUNG		G.U.		LYMPH NODE		BONE & JOINT	
		Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
ACUTE MILIARY	22	1	0	7	3	5	2	0	1	3	0
MILIARY FOLLOWED BY MENINGITIS	10	0	2	1	3	1	2	0	0	1	0
COMBINED MILIARY & MENINGITIS	25	0	1	2	12	1	2	1	4	1	1
MENINGITIS	43	3	1	10	21	1	1	2	3	0	1
TOTAL	100	4	4	20	39	8	7	3	8	5	2

the presence of acid-fast bacilli at some time before or during treatment, and classical clinical evidences of either central nervous system infection or meningitis or both.

**Miliary Tuberculosis.** Twenty-two patients (Tables 3 and 4), with acute disseminated miliary tuberculosis, but without meningitis, received treatment with streptomycin. Sixteen (73%) are alive after receiving, with one exception, from 116 to 157 days' continuous therapy with streptomycin, and have been observed for from 1 to 12 months

cystoscopy in 3 and a spinal fusion in 1. The remaining 4 patients had other and varying initial complaints.

The daily dosage of streptomycin was quite constant. Thirteen patients received 1.8 to 2 gm. streptomycin daily. One individual received 3 gm. throughout his course. Eight received 3 or 4 gm. daily for from 7 to 30 days at the beginning of treatment, to combat the acute toxicity of the disease; thereafter the daily dose was reduced to 1.8 gm. for the remainder of the

TABLE 3  
Acute Miliary and Meningeal Tuberculosis Treated with Streptomycin:  
Summary

Type of Disease	Total	DEAD			LIVING		
		Following Treatment Days		Total	Following Treatment Days 120-190	Treatment Terminated	Total
		1-44	45-180				
Acute Disseminated Miliary	22	3	3	6 (27%)	0	16	16 (73%)
Onset Meningitis During or After Therapy for Miliary	10	3	4	7 (70%)	1	2	3 (30%)
Combined Miliary and Meningitis	25	14	6	20 (80%)	0	5	5 (20%)
Meningitis	43	16	11	27 (63%)	1	15	16 (37%)
TOTAL	100	36	24	60 (60%)	2	38	40 (40%)

thereafter (average, 4.1 months). One individual completed but 67 days' treatment and was subsequently lost to the study. At the completion of therapy, he had active renal tuberculosis, although his pulmonary miliary lesions were regressing.

Fever was the first symptom in 14 of the cases. In 4 patients, surgical manipulations, which might have been the exciting incident in the hematogenous dissemination, had been performed from 2 to 9 weeks prior to the institution of therapy: namely,

treatment period. All streptomycin was given intramuscularly in 5 or 6 divided doses daily.

**The Dead.** Six patients died (Table 4), 4 of whom were receiving streptomycin at the time of death.

Three of the 6 had shown impressive improvement shortly after streptomycin was started. Acute toxicity disappeared in all 3; the miliary lung lesions regressed appreciably in 2, and were completely resolved at the end of 3 months' treatment in 1. The urinary bladder ulcerations in one case,

and the laryngeal lesions together with pulmonary infiltrations in another, cleared remarkably; in the third case fever dropped from daily spikes of 105 degrees to normal in 15 days. In spite of continued therapy, however, 1 of the 3 patients relapsed after 45 days' treatment and died with actively progressive tuberculosis. Death, imminent in the other 2 at the end of 4 months' treatment, occurred 3 and 4 weeks after its termination.

The autopsy of the patient who had received 45 days' treatment revealed many miliary pneumonic foci in the lung. The tubercles were atypical in the sense that the majority consisted

of large caseated centers with little or no peripheral fibrous reaction; giant cells were infrequent. There were only a few areas of fibrosis, with contraction and minimal distortion of the surrounding alveoli, and there were rare hyaline clumps. Stains for acid-fast bacilli revealed numerous organisms in all areas of caseation. Similar acutely caseating tubercles were found in the liver, spleen, adrenals, lymph nodes, kidneys and pancreas. The majority of these also were characterized by an absence of fibrosis and by an unusually large number of both intra- and extra-cellular acid-fast bacilli.

In contrast to this result, the post-

TABLE 4  
Acute Generalized Miliary Tuberculosis Treated with Streptomycin\*

		Number of Patients (22)	
		Living (16)	Dead (6)
DURATION OF ILLNESS PRIOR TO THERAPY (weeks)	range average	1 to 17 4.6	3 to 11 6.0
DAILY INTRAMUSCULAR DOSE OF STREPTOMYCIN (grams)	range average	1.8 to 4 2.2	1.8 to 4 2.3
TOTAL TREATMENT (grams)	range average	136 to 315 239	8 to 230 126
(weeks)	range average	9.5 to 22.5 18	0.5 to 21 11
SURVIVAL FROM ONSET OF ILLNESS (weeks)	range average	17 to 56 38	0.5 to 22.5 16.6
RESULTS OF TREATMENT			
Clinical:			
Afebrile and asymptomatic		12	0
Improved but continuing symptoms		4	0
Temporary improvement followed by relapse and progression		0	3
No effect, or progressive symptoms		0	3
Pulmonary Miliary Lesions:			
Complete regression		9	0
Resolution continuing		5	0
Temporary improvement followed by relapse and progression		1	3
No effect, or worse		1	3
Pre-existing Tuberculous Lesions:			
Arrested		5	0
Improved		7	2
Active and progressive		3	4
NEW LESIONS DEVELOPING DURING OR AFTER THERAPY			
		1 (epididymitis)	1 (empyema)

\* All patients received only one course of treatment. There have been no clinical or roentgenographic relapses in the surviving cases following cessation of therapy.



mortem findings of another patient, who had received 120 days' treatment with streptomycin, revealed great numbers of hyaline clumps and fibrotic nodules, which presumably represented healed remnants of tubercles. There were, in this individual, a few miliary lesions with caseated centers, but fibrosis was well established around each. Active and extensive tuberculosis was found in the lung and there was no evidence that streptomycin had affected this old and pre-existing lesion.

The remaining 3 individuals who died had all received streptomycin for less than 40 days and none had shown any response to treatment although it was being continued at the time of death.

*The Living.* Of the 16 patients still living (Table 4), all evidences of the acute complication have disappeared in 9, including resolution of the pulmonary miliary lesions. Five others have shown marked and continuing roentgenographic improvement but resolution of the miliary lesions is not yet completed. Two of these 5 continue to have evidences of active tuberculous infections in lung and bone. The remaining 2 patients, although improved clinically, continue to have evidence of active infection and the miliary lesions have shown little tendency to regress. One of these 2 has recently gone into a terminal uremic state, presumably due to an irreversible and bilateral renal tuberculosis.\*

During the 4th month of the post-treatment observation period, one patient developed a new lesion in the epididymis, a sinus opened and is now discharging tubercle bacilli. Despite this complication, no new evidences of an acute tuberculous dissemination have appeared. Re-treatment will be

instituted if the organisms prove to be still sensitive to streptomycin.

Resolution of the miliary lesions followed a similar pattern in all the patients in whom it occurred, the majority regressing completely in from 90 to 140 days. The case history of one patient will describe a result characteristic of the series.

**Case Report. No. 1.** Patient T. M., Veterans Administration Hospital, Washington, D. C., a 50-year old white male, had pulmonary tuberculosis since 1928. Between that year and 1946, there was slow and gradual roentgenographic progression of the process, but it had never become incapacitating. He had refused all treatment, had been able to work at odd jobs and he denied symptoms except cough during that period. On September 20, 1946, there was an abrupt onset of spiking fever, headache, and malaise, and at the time of hospital admission, 6 days later, the patient had become acutely and seriously ill.

Roentgenogram of September 26, 1946, showed bilateral, advanced, fibro-calcific and cavernous tuberculosis in both upper lung lobes, particularly on the left. A diagnosis of miliary tuberculosis could not be made at that time (Figure 1a). Early in October, however, roentgenograms clearly revealed finely disseminated miliary lesions throughout both lung fields (Figure 1b).

During the early period of his hospitalization, the patient's course was stormy, with daily temperature elevations to 103 and 104° F., and his physical condition deteriorated rapidly. Streptomycin was started October 8, 1946, 0.5 gm. intramuscularly every 4 hours (3 gm. daily). This dosage was maintained for 1 week. For the succeeding 113 days he received 0.3 gm. every 4 hours (1.8 gm. daily).

Within 10 days following the onset of treatment, the patient's temperature had dropped to below 100° F., he had noted immediate increase in appetite, and ma-

\* Since the preparation of this report, this individual has died. Death occurred 6 months following the onset of his miliary tuberculosis. He received streptomycin for 5 months. Progressive pulmonary and renal tuberculosis with uremia were the direct causes of death.

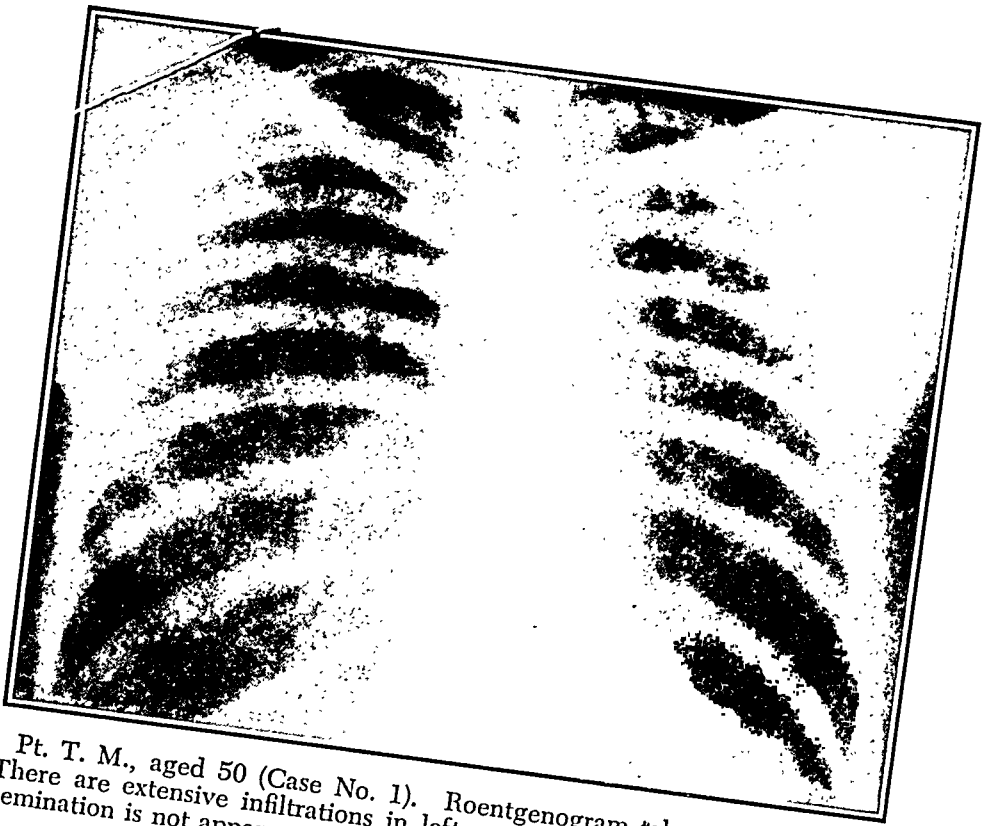


Fig. 1a. Pt. T. M., aged 50 (Case No. 1). Roentgenogram taken 9-26-46 on admission to hospital. There are extensive infiltrations in left upper lobe and in upper half of right lung. Miliary dissemination is not apparent. There has been calcification in left.

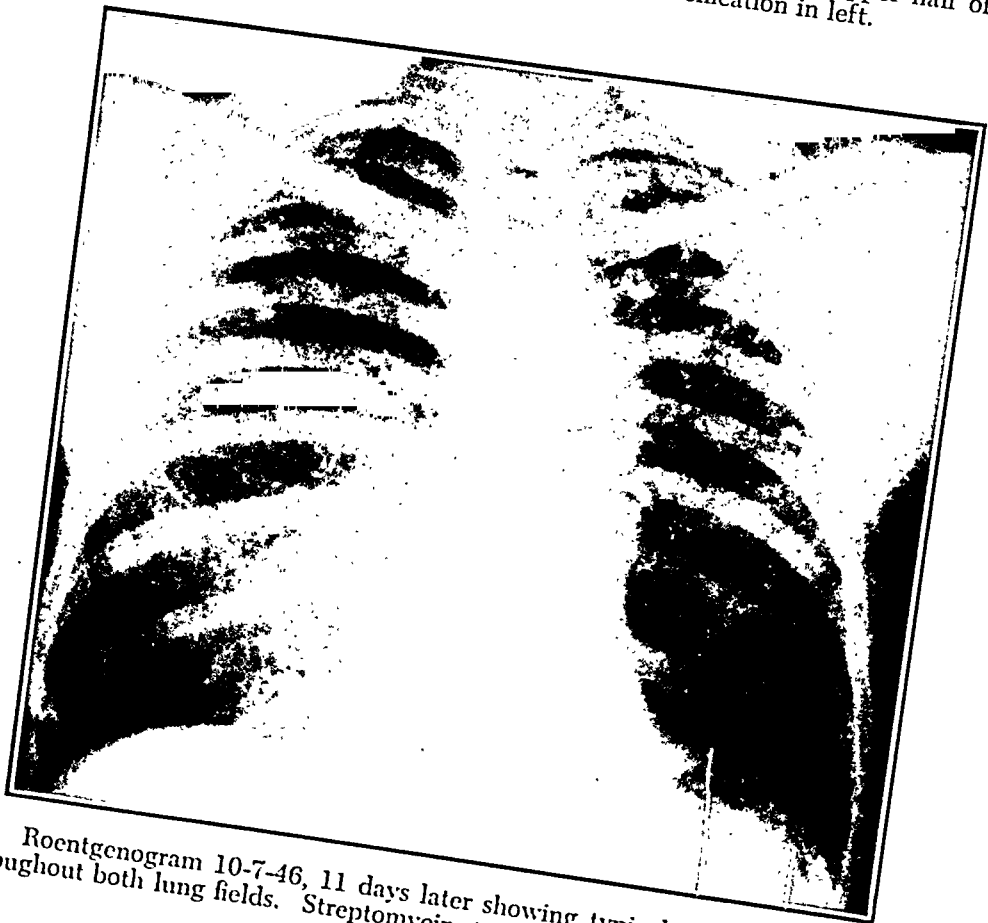


Fig. 1b. Roentgenogram 10-7-46, 11 days later showing typical diffuse miliary tuberculous lesions throughout both lung fields. Streptomycin started the following day.



Fig. 1c. Roentgenogram 11-25-46 taken 48 days after streptomycin was started. Individual pulmonary seedings are more punctate although there probably has been no resolution.

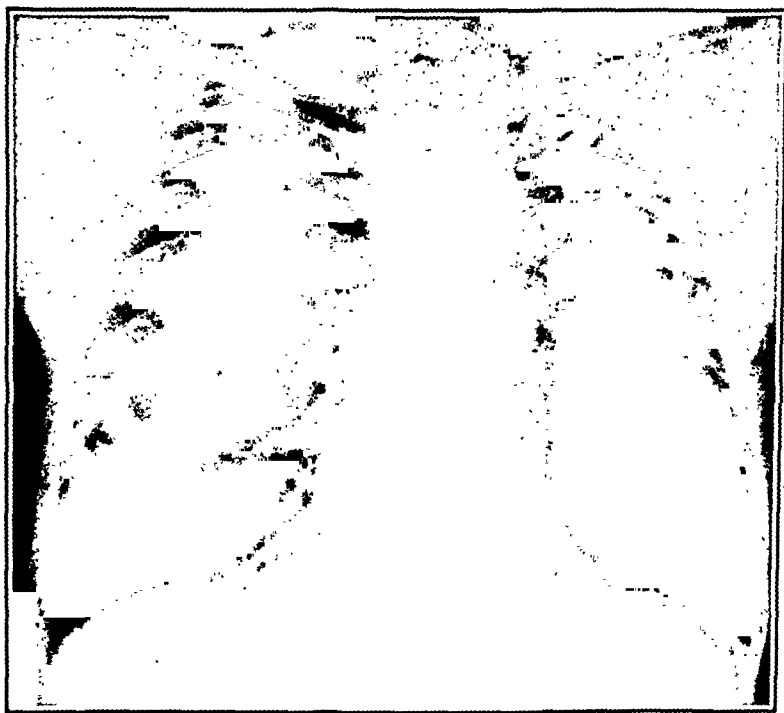


Fig. 1d. Roentgenogram 1-15-47 taken after 98 days of treatment shows marked improvement with resolution of the majority of miliary tubercles and a diminution in size of those remaining.



Fig. 1e. Roentgenogram 2-3-47 at the end of 120 days treatment. Resolution has continued so that miliary lesions are difficult to identify.



Fig. 1f. Roentgenogram 9-10-47, one year after admission to hospital and seven months after cessation of therapy. Miliary lesions remain healed. Pre-existing tuberculous disease in right lung has resolved markedly, but there remains an advanced fibro-calcific and cavernous lesion in the left. Patient has been ambulatory since end of therapy.

laise had disappeared. Within 7 weeks of the onset of treatment, his temperature had returned to normal, he had gained 6 pounds in weight and had become asymptomatic except for a hacking cough. At the end of 2 months' therapy the patient could not be kept in bed, and at the end of 4 months he could not be kept in the hospital. At the time streptomycin was discontinued, February 8, 1947, the patient had gained about 20 pounds and felt well; his cough was still productive of 15 cc. muco-purulent sputum daily.

Roentgenograms taken during October and early November showed no improvement. The film of November 25, 1946, (Figure 1c), however, revealed the punctate miliary infiltrations to have become more distinct. During December and January, there was a gradual reduction in the dimensions of each seeding and a diminution in their numbers, but the changes were not marked (Figure 1d). After the middle of January (3 months of therapy), the progress of the resolution became more rapid and by the end of the treatment period only sparsely scattered opacities could be seen (Figure 1e). Seven months later there had been no further change (Figure 1f). In the period of therapy and thereafter, the original pulmonary lesions had shown gradual clearing, although an advanced cavitory lesion remains in the left upper lobe.

Positive sputum smears were obtained throughout the course of therapy but whereas many organisms were seen in each microscopic field early in the course of therapy, later specimens had to be concentrated to find a few. The specimen obtained before streptomycin was administered contained organisms sensitive to 0.3 microgram streptomycin per cc. Those found after 90 days' exposure were resistant to 500 micrograms. A single specimen taken 3 months after the termination of therapy contained similarly resistant organisms.

After 2 months of treatment, audiometric examination disclosed a loss of hearing in the high tones, more marked in the left ear. At the end of treatment, there had been a further slight increase in this hearing loss. Seven months later,

in September 1947, there had been but minimal return of hearing in the high tones. Hearing in the conversational range had never been affected.

Throughout the course of treatment the patient neither complained of labyrinthine symptoms, nor were the results of the caloric test abnormal. Not until June, 1947, 4½ months after the cessation of therapy, was there a delayed response to caloric stimulation, nystagmus being only noted 90 to 145 seconds following stimulation of the middle ear with cold water. This finding has persisted. At the present time the patient is able to walk in a straight line with his eyes open, although somewhat slowly and hesitantly. His muscle tone is good, Romberg test is normal, and no other abnormalities are noted. He cannot walk in the dark, however, has fallen down steps twice, and has difficulty in focusing his eyes when he is moving about.

In summary, this 50-year old white male with long standing active and slowly progressive pulmonary tuberculosis recovered in a striking manner from an acute generalized miliary tuberculosis and is apparently cured of that complication 7 months after the cessation of streptomycin. Complete loss of vestibular function and minimal hearing loss are permanent residuals of that therapy. The miliary lesions were somewhat slower in resolving than is the case with most, but the process was completed within 140 days after the start of specific therapy.

**Summary of Results in Miliary Tuberculosis** (Tables 3 and 4). Twenty two individuals, all with clinical and roentgenographic evidences of acute miliary tuberculosis, but not meningitis, received streptomycin therapy. Three died during therapy without showing any response to treatment. Three others who had had an impressive clinical and roentgenographic response early in the course of therapy, relapsed while it was continued, or within 4 weeks of its cessation, and died. Sixteen patients are still alive. One is in the terminal stages of tuberculosis

(pulmonary and renal) and another has not shown significant improvement. The roentgenographs of 9 individuals have shown complete resolution, and marked reduction in size and number of the seedings has taken place in the remaining 5 patients. The associated foci, originally present in 15 of the 16 survivors, have shown regression in 7, as measured by laboratory or roentgenographic procedures, and in 5 others they have become arrested. In the remaining 3, the lesions have con-

tinued to be active and are apparently progressing. A new lesion (epididymitis) developed in one patient 4 months after therapy had been discontinued.

**Miliary Tuberculosis Followed By Meningitis During or After Therapy With Streptomycin.** Tables 3 and 5 summarize the results of treatment in 10 patients who were treated for miliary tuberculosis but who, during or after that therapy, developed meningitis.

TABLE 5

Acute Miliary Tuberculosis Followed by Meningitis during or after Treatment with Streptomycin

		Number of Patients	
		Living (3)	Dead (7)
DURATION MILIARY PRIOR TO TREATMENT (weeks)	range average	1 to 12 5.2	3 to 8 5.3
DAILY INTRAMUSCULAR DOSE OF STREPTOMYCIN (grams)	range average	1.8 to 4 2.6	1.8 to 4.5 2.7
SINGLE INTRATHECAL DOSE OF STREPTOMYCIN (grams)		0.1	0.02 to 0.2*
TOTAL TREATMENT (includes second courses in four patients)			
Intramuscular: (grams)	range	315 to 520	60 to 322
	average	462	212
(weeks)	range	24 to 38	5 to 28
	average	30.1	15.3
Intrathecal: (grams)	range	7.6 to 12	0.5 to 13.5*
	average	9.9	5.9
(number of injections)	range	71 to 135	5 to 125
	average	99	49
SURVIVAL FROM ONSET OF MILIARY (weeks)	range average	38 to 52 46	5 to 36 17.3
ONSET MENINGITIS			
Under Treatment (3 to 8 weeks)		1	5
Following Cessation of Treatment (3 to 14 weeks)**		2	2
RESULTS OF TREATMENT			
Clinical:			
Asymptomatic		1	0
Temporary remission followed by relapse		2*	5
No effect		0	2
Pulmonary Miliary Lesions:			
Complete regression		3	4
Resolution continuing		0	1
Temporary regression during treatment followed by progression		0	1
No effect		0	1
Pre-existing Tuberculous Foci:			
Arrested		1	0
Improved		1	2
No change, or worse		1	3

\* One patient received no streptomycin intrathecally.

\*\* First courses of treatment in these four were from 90 to 195 days.

Seven of the 10 patients have died, another is in the terminal stages of meningeal tuberculosis\* and the 9th patient has far advanced progressive pulmonary tuberculosis, in addition to severe residual brain damage caused by the meningitis and encephalitis. He has, however, recovered from evidences of central nervous system infection. Only one patient is entirely free of signs and symptoms of infection.

Prior to the development of meningitis, streptomycin was administered only by the intramuscular route, in 5 or 6 doses each day. Six of the 10 patients received 1.8 to 2 gm. daily throughout the course of therapy. Three others received 3 or 4 gm. daily for 10 to 30 days at the outset and then 2 gm. a day for the remainder of their course. One patient received 3 to 4.5 gm. daily throughout the duration of treatment.

Although seeding in the central nervous system may well have occurred at the time the original massive dissemination took place, there was no clinical evidence of meningitis when therapy for the miliary lesions was undertaken. Lumbar punctures revealed normal spinal fluid in 3 patients early in the course of their treatment. There is no evidence, in these instances, that the procedure affected the subsequent development of meningitis.

Although, on the face of it, the end results of streptomycin therapy in this series represent at least 90% failure, they were, until the time when signs and symptoms of meningitis developed, quite as favorable as those in the preceding series. Eight of the 10 patients showed marked clinical improvement within 30 days of initiating treatment

and roentgenographic evidence of the pulmonary dissemination regressed in all 8 and disappeared altogether in 3 of them. The other 2 patients did not respond either clinically or roentgenographically.

Clinical meningitis became obvious in from 3 to 8 weeks after the institution of treatment in the 6 patients in whom it developed while therapy was being continued for the miliary disease. In 5 of these, intrathecal streptomycin was added to the regimen; in the 6th, no intrathecal streptomycin was used. In contrast to the striking response to treatment of their miliary disease, improvement in signs and symptoms of the central nervous system infection did not occur in any of these 6 patients. Five of them died and, although the 6th is still alive, he has had irreparable brain damage and is not likely to survive.

Four patients developed meningitis after their treatment for miliary tuberculosis had been completed. The miliary lesions of all 4 had disappeared, the patients were asymptomatic, and 3 were being rehabilitated at the time the central nervous system infection developed. This took place abruptly, and without other evidence of a fresh dissemination, 3, 4, 10, and 14 weeks after the administration of streptomycin had been stopped. Clinical response to a renewal of streptomycin therapy was negligible in 3 instances, 2 patients dying, and a 3rd being barely alive 12 weeks after it was recommenced.

Pathological studies on patients in whom death was delayed and in whom there had been roentgenographic improvement in the pulmonary lesions during life showed definite effects of

\* This individual died in November, 1947, 10 months after the onset of his miliary tuberculosis and 8.5 months after the onset of meningitis. He received 5.5 months of continuous therapy.

\* Gross and microscopic sections of tissues from this patient were reviewed for us by Drs. Webb Haymaker, Army Institute of Pathology, Emil Bogen, Olive View, California, and Max Pinner, Berkeley, California (Page 297, line 1).

streptomycin therapy. In one patient\*, for example, neither tubercles nor giant cells were seen in the lung. There were areas which consisted of mononuclear cells, lymphocytes, large epithelial cells and fibroblasts, but the arrangement of these did not suggest tuberculous lesions. There were, in addition, many areas of hyalinization with surrounding collections of collagenous tissue and these were infiltrated with small round cells, probably lymphocytes. The morphology of these differed from spontaneously healed tubercles because of the absence of definite encapsulation. These lesions have been described previously by Baggenstoss *et al.*<sup>1</sup> and probably represent advanced if not complete healing of tubercles following the effective use of streptomycin. Areas similar to this were found in liver, spleen and tracheobronchial lymph nodes.

Evidences of active tuberculosis were, however, found in the brain and kidney of this individual. In the kidney, there were large caseating tubercles with some conglomeration, an absence of fibrosis and fibroblasts and minimal numbers of giant cells. In each of these areas there were great numbers of acid-fast bacilli. In the brain, cerebral and arachnoid abscesses were seen, although the evidence for these being tuberculous was not conclusive. In addition to them, however, there were an adhesive arachnoiditis, internal hydrocephalus and meningitis. The meningeal lesions were characterized by an absence of fibrosis and giant cells. There was marked endothelial proliferation of all vessels in the involved leptomeninges and extensive caseation, particularly in the pia. Caseo-necrosis was also observed within the brain substance adjacent to a large flat abscess over the base of the brain.

**Summary of Results in Miliary Tuberculosis Followed by Meningitis.** Ten individuals, originally treated for miliary tuberculosis with intramuscularly administered streptomycin, developed meningitis (Tables 3 and 5). In 6, the central nervous system complication became apparent 3 to 8 weeks after the start of streptomycin treatment and while it was being continued. Five of these patients died, the administration of streptomycin being without apparent effect upon the meningitis. One patient survives but has had irreparable brain damage, is deaf, and has terminal tuberculosis elsewhere. Four patients developed tuberculous meningitis 3 to 14 weeks after the cessation of treatment for the miliary lesions. The onset of meningitis, although abrupt in all, was not associated with manifest generalized re-dissemination of tubercle bacilli. Two of these patients died within 8 weeks, the reinstitution of streptomycin therapy proving ineffective. A third continues to vegetate after 100 days' treatment in the second course and is not likely to survive. Only one patient, the 4th, survives and is apparently in complete remission from both miliary and meningeal tuberculosis, albeit his spinal fluid is still abnormal in respect to cell count and protein concentration.

In contradistinction to the ineffectiveness of streptomycin upon the meningeal lesions, the miliary lesions in 8 of the 10 patients resolved markedly or completely during therapy and, prior to the development of meningitis, all of them had shown marked clinical improvement. This contrast should be susceptible of explanation. The most rational suggestion is that the tubercle bacilli, initially sensitive to streptomycin and thereby allowing the host to heal the pulmonary seedings, had become resistant to the drug at the time the meningeal process developed



and the progression of this process to a fatal termination was a consequence of this resistance. That such a resistance, as judged by *in vitro* determinations, develops in approximately 25% of patients treated with streptomycin for 60 days and in approximately two-thirds of patients treated for 120 days is common knowledge<sup>3</sup>. And it is consistent with this suggestion that the only 2 patients of this group upon

whom determinations were made had organisms which were resistant to 1000 mcg. of streptomycin per cc. at the time meningitis developed. Both patients died. The suggestion, however, remains a suggestion.

Experience with this group indicates that the development of meningitis is the most serious complication of miliary tuberculosis and emphasizes the importance of routine spinal fluid ex-

TABLE 6

Combined Miliary and Meningeal Tuberculosis Treated with Streptomycin

		Number of Patients Living (5) Dead (20)	
DURATION OF COMBINED DISEASE PRIOR TO TREATMENT (weeks)	range average	1 to 4.5 3.1	0.2 to 8.5 2.2
DAILY INTRAMUSCULAR DOSE OF STREPTOMYCIN (grams)	range average	1.8 to 4 2.3	1.8 to 4 2.2
SINGLE INTRATHECAL DOSE OF STREPTOMYCIN (grams)		0.01 to 0.1	0.02 to 0.2*
TOTAL TREATMENT			
Intramuscular (grams)	range average	189 to 490 320.6	4.1 to 253 120.1
(weeks)	range average	12 to 30 22.2	0.3 to 18.1 8.6
Intrathecal (grams)	range average	1.6 to 15.1 9.4	0.125 to 8 3.4
(number of injections)	range average	22 to 140 91	6 to 110* 62
SURVIVAL FROM ONSET OF COMBINED DISEASE (weeks)	range average	25.7 to 77.1 31.7	0.3 to 21.4 9.3
RESULTS OF TREATMENT			
Clinical:			
Asymptomatic at termination of first course of treatment		4	0
Temporary remission during treatment followed by relapse		0	5***
No effect		1	15
Pulmonary Miliary Lesions:			
Complete regression		4	4
Resolution continuing		1	0
Temporary regression during treatment followed by progression		0	4
No effect		0	12
Pre-existing Tuberculous Foci:			
Arrested		1	0
Improved		3	4
No change		1	16
Relapses following cessation of therapy		2**	0
Time of appearance after cessation (weeks)		6 and 7	0
Duration first course of treatment (weeks)		12 and 16	0

\* Two patients did not receive streptomycin by the intrathecal route.

\*\* Both have active meningeal tuberculosis after completing a second course of treatment of from 3 to 4 months.

\*\*\* All relapses were meningeal. Reappearance of pulmonary miliary lesions was not observed.

amination so that this complication may be diagnosed and the intrathecal administration of streptomycin be started, as early as possible.

**Combined Miliary and Meningeal Tuberculosis.** In contradistinction to the previous group, this series of 25 patients (Tables 3 and 6) had evidences of both acute miliary tuberculosis and tuberculous meningitis at the time therapy was instituted and treatment was directed toward both complications from its inception.

Twenty of the 25 patients died, 14 (56%) within the first 6 weeks (average survival from onset of illness 8 weeks), and 6 after surviving for more than 2 months (average 15 weeks). Five are still living, with an average survival of 7.4 months since therapy was started.

Nine patients received 1.8 to 2 gm. streptomycin daily for 120 days, 10 others received 3 to 4 gm. for from 14 to 90 days, before the daily dose was reduced to 2 gm., and 6 patients received 2.4 to 3 gm. throughout the course of treatment. Twenty-two of the 25 patients received from 0.02 to 0.2 gm. streptomycin intrathecally daily or every other day, at least during the first month of therapy or until death supervened.

Three patients received either inadequate intraspinal therapy or none, and all died. The demise of one occurred after 7 days' intramuscular therapy. The diagnosis of meningitis in another was never confirmed until late in the course of therapy and 6 intrathecal injections did not alter the progressive course of the combined disease. The 3rd patient did not receive streptomycin intrathecally because the necessity for its administration by this route was not appreciated at the time of his illness. His combined disease had been diagnosed early in its in-

ciency and intramuscular therapy promptly instituted. The meningeal disease improved markedly for 90 days despite the omission of intrathecal medication but he never became completely free of evidences of central nervous system infection. His sensorium cleared considerably with therapy, his hyperirritability and occasional delusions were partially relieved, and the spinal fluid cell count, never greater than 90 cells, was reduced to 20 on one occasion. The explanation for this improvement may rest with the observation that spinal fluid concentrations of streptomycin of the order of 4 to 10 micrograms per cc. were assayed periodically during his treatment course. During the 4th, and last, month of treatment with streptomycin, however, neurologic disorders became more manifest and mental deterioration occurred. At autopsy the gross and microscopic findings from the tissues of this individual\* were typical, in general, of those in the other 12 patients who died after receiving appreciable amounts of streptomycin. Within the lung, there were only occasional foci of caseation necrosis. Some of these had central calcification with dense fibrous capsules and a few Langhans giant cells. Considering the typical dense miliary seedings which were seen by roentgenograph during life, these observations were quite remarkable for a majority of the hematogenous lesions had apparently either disappeared or been completely healed. Elsewhere evidences of active tuberculosis of the miliary type were prominent. Caseous foci with minimal fibrous reaction were found in the kidneys, prostate, liver, spleen and tracheobronchial and abdominal lymph nodes. Within the thorax itself all mediastinal glands were caseous structureless

\* Details of this case will be the subject of a future report from the Veterans Administration Hospital, Van Nuys, California.

masses. In none of the lesions outside the lungs was there any evidence of healing, or of a specific streptomycin effect. Active tuberculous meningitis and encephalitis were present, as were adhesive arachnoiditis and internal hydrocephalus. The leptomeninges were covered with a pale green-grey fibrinous exudate, particularly at the base of the brain.

Streptomycin did not produce any beneficial effect in any of the 14 patients who died within 6 weeks of beginning treatment nor in 1 who died after receiving 9 weeks' treatment. In general, at the start of treatment, these patients were in terminal stages of pulmonary tuberculosis and, although the duration of the acute complication was relatively short in a majority, streptomycin could scarcely have been expected to alter the rapidly fulminating nature of the infection. In all, the course was one of progressive deterioration without true improvement in either signs or symptoms. The sensitivity of the organisms to streptomycin was not determined.

The meningeal signs and symptoms in 5 patients who received more than 6 weeks' treatment with streptomycin, were alleviated markedly during the first weeks of therapy, but in none were the improvements maintained, and in none was there a complete recovery from all evidences of neurologic disease. The pulmonary miliary lesions of healed tubercles described by Baggenstoss<sup>1</sup> and McDermott<sup>6</sup> were found at autopsy in 4 cases. The pulmonary miliary lesions in the 5th cleared by roentgenogram after 60 days' therapy but thereafter a relapse occurred and at autopsy, no evidences of healing, old or new, could be found amongst the myriads of necrotizing tubercles.

Five patients in this series of 25 survive. The best, but not atypical, response to treatment occurred in a

patient treated at the Veterans Administration Hospital, Van Nuys, California.

Case 2. This 36-year old white male was admitted to the hospital July 31, 1946. He gave a history of weakness, fever, chest pain, and cough, for 2 months. A diagnosis of pulmonary tuberculosis was made and the patient was placed upon a rest regimen. His sputum was positive. Except for 2 periods of fever in September, and again in November and December, 1946, he was more or less asymptomatic until February, 1947.

During that month the patient noted cephalalgia and aching in the muscles of both legs. Thereafter he became febrile, listless, and lost his appetite. Roentgenogram on the first day of fever showed a diffuse miliary spread throughout all lung fields and a lumbar puncture 2 days later revealed the spinal fluid under pressure of 215 mm. of water and with 46 cells (44% neutrophils). Acid-fast bacilli were seen on smear. Streptomycin was started, 1.8 gm. intramuscularly and 0.1 gm. intrathecally 3 days after the onset of fever.

Within one week, daily temperatures, which had spiked to 101.5° F., dropped to normal and remained normal thereafter except for isolated and temporary elevations. Headache, stiff neck and listlessness disappeared within 6 weeks. Intraspinal therapy was discontinued after the 44th day of treatment because of an episode of disorientation and irrationality which was thought to be related to the injection of streptomycin. Following this, his course again became one of continued improvement. Intramuscular therapy was stopped after 115 days because of a questionable renal damage although subsequently this could not be proved.

For the first 4 weeks of therapy there were not discernible changes in the pulmonary roentgenograms. During the 5th week, the miliary infiltrations throughout both lungs became more discrete, less dense, and there was considerable clearing of the chronic pulmonary process in the left upper lobe. After 2 full months of therapy, the lesions had regressed almost to the point of complete clearing. When treatment was stopped, the miliary lesions

could be only vaguely seen. The chronic pulmonary process, following an initial improvement, remained unchanged after the second month.

Minimal, bilateral hearing loss (6 decibels) occurred early in the course of treatment but did not progress. Two months following cessation of streptomycin, no loss could be detected in the left ear and only a loss of 4 decibels in the right.

During the period of intrathecal therapy, spinal fluid cell counts remained above 50 cells and the protein above 100 mg. per 100 cc. The sugar was normal throughout. Following cessation of intraspinal therapy, the cell count gradually returned to more normal levels and at the end of treatment was 12 cells, all lymphocytes. The protein, on the other hand, did not fall below 60 mg. per 100 cc. until 2 months after cessation of therapy. At the present time, the cell count is 12, sugar 90 mg., total proteins 58 mg., and the fluid is under normal pressure. Acid-fast bacilli were found in 3 specimens, taken prior to and shortly after the start of therapy. After the 2nd week of treatment, it remained sterile by smear and culture.

At the present time, 3 months after cessation of treatment, the patient is still confined to bed because of continued activity of his pulmonary tuberculosis. He has no fever, raises small amounts of muco-purulent sputum daily, has a fair appetite and his weight, after gaining 15 pounds during therapy, is now stationary. He has mild occipital headaches but they occur infrequently; otherwise there are no abnormal signs or symptoms of nervous system disease.

Evidences of active infection in the central nervous system disappeared similarly in 2 other of the 5 patients who have survived. The neurological signs improved, the mental disturbances were promptly relieved, and the spinal fluids became sterile. Deferescence occurred by rapid lysis in from 7 to 14 days. The spinal fluid constituents failed to become entirely normal in the sense that cell counts

remained above 60 and protein concentrations above 100 mg. per 100 cc. There was no apparent tendency for these values to become less during the period of therapy. The impressive degree of improvement in these 2 patients was not, however, maintained and, 6 and 7 weeks, respectively, after the conclusion of the 1st course of treatment, signs of meningeal infection recurred. Although organisms could not, on this occasion, be demonstrated in the spinal fluids, streptomycin therapy was reinstituted and continued for 90 and 120 days. In one patient, this second course of treatment was without effect; he continues to be febrile with grossly abnormal spinal fluid; he is semi-stuporous and has developed evidence of increased intracranial pressure. The other patient was relieved of the signs and symptoms of acute meningitis by the second course of treatment but he became mentally sluggish and incontinent of urine and feces.

In the other 2 surviving patients, the accessory evidences of infection, (that is, leukocytosis, fever, and general appearance of acute toxicity), disappeared similarly but the end results were unsatisfactory. In one, the state of profound coma failed to diminish, neurological signs which included 2nd and 6th cranial nerve palsies were unaltered and, during the treatment period, he developed additional evidence of severe brain damage. At the end of 6 months' treatment, he was free of infection in the central nervous system but was decerebrate and, for a great part of the time, remained semi-stuporous. He has continued in this state for the 3 months which have intervened since cessation of therapy. The 5th patient had a better response to treatment in the sense that signs of active tuberculosis in the central nervous system were reduced, but he was left with a residual 4th cranial nerve palsy and some indications of irreversible brain

damage. He has progressing and advanced pulmonary tuberculosis which was affected little if at all by the streptomycin.

**Summary of Combined Miliary and Meningeal Tuberculosis.** Twenty-five patients with acute miliary tuberculosis and tuberculous meningitis have been treated with streptomycin (Tables 3 and 6). Fourteen patients died within 6 weeks of the onset of treatment without streptomycin having exerted any demonstrable effect upon their clinical course or upon the pathology of their lesions. This high percentage of early deaths (56%) cannot logically be attributed to the development of a resistance to streptomycin in these cases and all that one can say is that the infection was so overpowering and widespread as to make the drug useless. Veterans Administration hospitals are, at the moment, exploring the effects of larger doses of streptomycin and of combined streptomycin-promin therapy on this type of case.

Six of the remaining 11 patients have died. In 1 of these, streptomycin was without benefit. A marked clinical improvement occurred in the other 5 but it was not maintained despite continued treatment and death in all 6 occurred 6 to 20 weeks after the start of therapy. Five are still living, of whom 2 have recently completed a 2nd course of therapy required by a recurrence of their meningitis; these 2 and 2 other patients treated continuously for 6 months are all doing badly. Only 1 patient of the 25 can be considered a therapeutic success.

Although the end results of streptomycin therapy in this group are, thus, very unsatisfactory, its ability to affect the tuberculous lesion has again been demonstrated. The lives of 10 patients were indubitably prolonged by streptomycin and in 8 of these the pulmonary dissemination, visualized by roentgenogram, cleared entirely. The pre-

existing sources of the dissemination were improved in 7 cases and arrested in 1. As was the case with the group described previous to this, the presence of meningitis *in addition to* pulmonary dissemination appears to be responsible for the high mortality rate.

It will be observed from Table 6 that no patient receiving less than 189 gm. streptomycin intramuscularly or less than 22 intrathecal injections of the drug has survived.

**Meningitis.** The most spectacular and decisive effect which streptomycin exerts upon the course of human tuberculosis is amply demonstrated by the results which have been obtained in the treatment of tuberculous meningitis<sup>1,5,6,8</sup>. Never before in the history of tuberculosis has any agent been able to lower the mortality rate appreciably below 100%. In the present series (Tables 3 and 7), 43 patients with proved tuberculous meningitis have been treated with streptomycin. Twenty-seven (63%) have died, 16 (37%) of them within 6 weeks of the start of treatment. Sixteen patients (37%) are alive 4 to 14 months after the institution of therapy.

The diagnosis in all cases was made by clinical evidences of meningeal irritation and the finding of morphologically characteristic bacilli in spinal fluid. The organisms were found by direct smear of the spinal fluid pellicle, by culture or guinea pig inoculation, at autopsy, or by all 3 methods. All patients were treated by both intramuscular and intrathecal routes.

**The Dead.** Of the 16 patients who died within 6 weeks of the institution of therapy, in none was there an appreciable response to treatment and in none was the spinal fluid sterile at the time of death. Many of them were temporarily relieved of headache and some recovered, also temporarily, from the coma which was initially present. Fever, ranging from 100 to 105° F., was

present in all 16 patients prior to treatment. It was dramatically lowered in 8, and to a lesser degree in the others. In none, however, was the clinical improvement maintained for longer than 2 weeks and in none did neurologic signs disappear after treatment was started.

Autopsies were performed on 8 of these 16 patients. Gross and microscopic findings demonstrated no effect of streptomycin upon the tuberculous pathology.

An additional 11 of the 43 patients, although dying eventually, survived for periods longer than 6 weeks. Nine died during a first course of therapy, after they had received streptomycin for an average of 3.3 months; the other 2 died 10 and 16 months after the commencement of treatment. There can be no question but that the use of streptomycin prolonged the life of these 11 patients. Nor is there any question about the prompt and striking amelioration of signs and symptoms which oc-

TABLE 7  
Tuberculous Meningitis Treated with Streptomycin

		Number of Patients	
		Living (16)	Dead (27)
DURATION MENINGITIS PRIOR TO TREATMENT (weeks)	range average	0.5 to 8.5 2.9	0.3 to 8.4 2.3
DAILY INTRAMUSCULAR DOSE OF STREPTOMYCIN (grams)	range average	0.6 to 3.0 1.9	1.2 to 4 2.4
SINGLE INTRATHECAL DOSE OF STREPTOMYCIN (grams)		0.02 to 0.2*	0.1 to 0.2
TOTAL TREATMENT			
Intramuscular (grams)	range average	155 to 375 268.6	3 to 390** 138.8
(weeks)	range average	11 to 25.3 18.9	0.3 to 26** 10.5
Intrathecal (grams)	range average	3.5 to 15.4 10.3	0.15 to 12.5** 4.1
(number of injections)	range average	45 to 150 90	2 to 125** 37
SURVIVAL FROM ONSET OF DISEASE (weeks)	range average	17.1 to 56 43.8	2 to 42.1** 16.5
RESULTS OF TREATMENT			
Clinical:			
Asymptomatic at termination first course of therapy		10	0
Temporary remission followed by relapse during first course of therapy		4	15
No effect		2	12
Pre-existing Tuberculous Lesions:			
Arrested		3	1
Improved		7	5
No change		5	20
RELAPSE FOLLOWING FIRST COURSE OF TREATMENT (2 patients, 5 relapses)			
Onset of relapse after cessation of therapy (weeks):	range—	2 to 13	
Duration first course of streptomycin (weeks)		8 and 10	
Duration second course of therapy (weeks)		21 and 21	
Duration third course of therapy (weeks)		5 and 0.5 (fatal)	
Duration fourth course of therapy (weeks)		11.5 (fatal)	

\* One patient received 0.5 gm. streptomycin intrathecally on 2 occasions.

\*\* Excludes patient who survived 16 months, who received more than 600 gm. streptomycin in 3 courses during that period, and who was given 288 intrathecal injections of 0.1 gm. streptomycin. For the greater part of his treatment the patient received 2.0 gm. streptomycin intramuscularly daily.

curred early in the course of treatment. To take a single dramatic example, 3 of the 11, who were in coma and apparently moribund at the time treatment was started, became afebrile and quite rational within 2 weeks. Relief of attendant symptoms also occurred in a number of these patients. Six had moderate to marked relief of distressing neurologic symptoms within 7 to 12 days following the institution of therapy, and this relief was maintained for an average of 60 days. Two of these 6 had, in addition, a reduction in symptoms due to associated tuberculous foci. In one, laryngeal lesions and advanced pulmonary tuberculosis had made the patient progressively uncomfortable for almost 6 months prior to the onset of meningitis. Within a few days of the start of treatment, both the disturbing cough and the dysphagia disappeared. In the other, a pulmonary lesion was markedly improved.

The 2 patients who survived for the longest periods (10 and 16 months) had received 2 and 3 courses of streptomycin, respectively, and were receiving their 3rd and 4th courses at the time of their death. Although they had made complete clinical recoveries from their initial attacks and earlier relapses, streptomycin was entirely without effect on their final relapse. It is presumably significant that tubercle bacilli, both from their spinal fluid and sputa, were resistant to 1000 mcg. per cc. during their last course of treatment. Unfortunately, similar data are not available during their earlier relapses. In neither patient did the spinal fluid ever become entirely normal.

The gross and microscopic studies of the meninges and brain of 8 of these 11 patients who were subjected to autopsy revealed analogous findings. The cerebrospinal fluids were all grossly cloudy and 4 were positive for tubercle bacilli. There was an active arachnoiditis over the base of the brain

in each, and in most there was a thick, often friable, fibrinous exudate extending over the pons and onto the cerebellum. In some, evidence of meningitis was found over the cerebrum. All vessels in the regions of disease were uniformly and largely engorged. The ventricular systems of 5 were dilated to some degree, although the choroidal plexi were apparently normal in 3.

Microscopically, the meninges in the involved areas were usually diffusely thickened and densely infiltrated with lymphocytes. Tubercles with epithelioid cells were found scattered throughout but most of them were well encapsulated. Central caseation was common and in a few there was beginning calcification. Infarcts due to thrombosed vessels were frequently seen and, in the regions of the tissue so destroyed, tuberculous lesions could be seen extending into the brain substance. Tuberculomas in brain substance, of indeterminate age and of various sizes, were found in 5 of the 8 patients, but in none were acid-fast bacilli found. Each was encapsulated although the centers were necrotic and caseating tubercles were found in the periphery of 3.

The most significant finding in the majority was the organization seen in the leptomeninges. Another significant observation was the rather marked amount of tuberculosis in the brain substance, most of which had apparently extended from overlying tuberculous processes in the meninges.

*The Living.* Sixteen patients in the series have thus far survived. Although it is quite possible that some, or even all, of them will eventually relapse and die, they have lived from 4 to 14 months after the onset of their illness (average 7.5 months) and the majority are, at this time, free of stigmata of central nervous system infection.

All patients (Table 7) received intrathecal streptomycin and during the

course of therapy from 45 to 150 single injections were given. The amount used per injection was usually 0.1 gm. but varied from 20 mg. to 500 mg. This latter dose was given twice to one patient and produced extremely severe nerve root pain on both occasions. The total amount administered by this route during the course of treatment varied from 3.5 to 15.4 gm. The intramuscular route was also employed and, with a single exception, each patient received at least 1.8 gm. daily, 3 were given 2.4 to 4 gm. during the first 1 to 4 weeks and 1 received 2.4 gm. daily for 150 days. Single courses of treatment, with one exception, extended from 115 to 180 days.

Tuberculous lesions outside the central nervous system in these patients were sometimes benefited by streptomycin. In 2 patients, pulmonary tuberculosis became arrested and in 4 others the lung lesions were considerably improved. Cutaneous sinuses healed in 1 patient and renal tuberculosis in another became quiescent so that a nephrectomy could be safely performed.

The common response to treatment can be best described by presenting a case report:

Case 3. F. McK., a 34-year old white male, was admitted to Veterans Administration Hospital, Dayton, Ohio on June 21, 1946, with a diagnosis of tuberculous meningitis. Pulmonary tuberculosis had been diagnosed 1 year previously and after a period of bed rest and the institution of a right pneumothorax at another hospital, he had, since early 1946, been an ambulatory patient. Symptoms at the time of admission in June were characteristic of meningitis—headache, blurred vision, stiff neck, nausea and vomiting. Their onset had been ushered in a few hours previously by a shaking chill and subsequent fever of 101° F. Physical examination revealed an acutely ill, irritable, white male with thick speech, slow cerebration and delayed response to stimuli. Nuchal rigidity was marked, deep reflexes

were absent and there was a positive Babinski sign. The spleen was not palpable. Laboratory findings showed a white cell count of 6000 and a normal differential. Spinal fluid on that day was positive for acid-fast bacilli, later proved by culture; it contained 139 cells, 80% of which were polymorphonuclear leukocytes, 37 mg. per 100 cc. sugar and the tryptophane test was positive.

During the next 8 days, the patient's temperature rose daily to 102°-103° F., projectile vomiting was common, and he was gravely ill. Streptomycin was started June 28, 1946, in a dosage of 2.4 gm. daily intramuscularly (.4 gm. every four hours) and 0.1 gm. intrathecally every other day.

The patient's general condition started to improve immediately. Within 1 month, fever was reduced to below 100°, headache, nausea and vomiting became less bothersome and the nuchal rigidity gradually relaxed. He became alert and his appetite returned. This degree of improvement was maintained until September. During this 2-month period, hearing loss was noted and when it was observed to be progressive 30 days after the start of treatment, the intramuscular dosage of streptomycin was reduced from 2.4 gm. to 0.6 gm. daily.

Early in September, streptomycin was discontinued for 5 days. Fever rose within 48 hours, vomiting started again, and the patient relapsed into a state of subacute but progressive illness. Because of these evidences of relapse, streptomycin was started in the reduced daily dosage (0.6 gm. intramuscularly and 0.1 gm. intrathecally) and continued without interruption until January 10, 1947. At the time the second course of streptomycin was started, spinal fluid cell count was over 100 (60% lymphocytes), the sugar had remained below 30 mg. per 100 cc. and the proteins were elevated. The fluid was, however, sterile.

During September and until mid-October, 1946, the patient became progressively worse, and it appeared that he would surely die. Intractable vomiting necessitated the use of parenteral feedings as well as gastric tube feedings. He lost weight and became listless and apathetic.



His fever continued above 100° and neurologic signs of ankle clonus, diminished peripheral vision, and sluggish reflexes were evident at all times. In the middle of October, without change in treatment program, this downhill course was gradually reversed (120 days after onset of his illness). He began to eat, and his complaints of blurred vision, diplopia and headache diminished. Mental alertness returned, his speech, previously thick, cleared and he was able to write and talk normally. By December first, he was asymptomatic and without evidences of neurologic abnormalities, able to walk about his room, shave and perform all simple muscular exercises. There was no fever. Spinal fluid early in December contained 18 cells. The sugar was normal for the first time since the first diagnostic lumbar tap but the proteins remained above 100 mg. per 100 cc. Sputum had become negative by smear and culture and although a pneumothorax hid details of his pulmonary disease, there appeared to have been improvement in that as well. This state of freedom from evidences of infection has continued to date.

In January, 1947, the patient complained more bitterly than usual about the shooting pains down his legs at the time of, and following, intrathecal injections of streptomycin. The physician, unable to demonstrate abnormalities on neurologic examination, continued the every-other-day injections until January 15. On that day, transient paraplegia developed following a spinal tap and it persisted for the next 48 hours. Despite it, a final injection was made. Following this, there was an acute exacerbation of the symptom complex, and a complete transverse myelitis, with loss of urinary bladder control, became apparent. Streptomycin was then discontinued (intramuscular streptomycin had been discontinued 1 week earlier), after a total of 168 gm. intramuscularly in 190 days (5-day lipse excluded) and 9.8 gm. intrathecally given in 98 injections over 195 days.

On January 18, the 1st day after therapy was stopped, the patient's neurologic examination was as follows: marked atonia and weakness of all muscles of the lower extremities, an unsteady gait, di-

minished deep reflexes and hypesthesia. Evidences of disturbed vestibular function and hearing loss were also present. Sensation was intact and reflexes were active elsewhere. Clinically, the patient was cheerful, his appetite was satisfactory, and he was afebrile. Intermittent, mild, daily, headaches were, however, a continued complaint. His pulmonary tuberculosis was considered quiescent.

One month later, the evidences of paraplegia had disappeared, the muscular weakness had improved, reflexes became equal and active, the unsteady gait improved and he learned to walk without support. Deafness, not apparent in conversational range, and the vestibular signs had, however, not improved.

Spinal fluid at the end of treatment revealed 40 cells and proteins above 100 mg. per 100 cc. Three months later, cell count had fallen to 10, all lymphocytes, and the protein had fallen to 70 mg. At last report, the patient was continuing in the same state of good health with normal spinal fluid cell count, but with slightly elevated protein concentration. In early June, 1948, he had survived almost 24 months and there were no evidences of active tuberculosis either of the lungs or central nervous system.

This case was unusual in the slowness of his response since, although the characteristic initial improvement occurred, the patient suffered a relapse and true recovery did not begin until well after the 90th day of treatment. It may be that the reduced intramuscular dosage which was employed ( $\frac{1}{2}$  or less than that used in the other cases) was responsible for the delay. This point aside, the clinical response of 9 other surviving patients was very similar. Two, having survived their meningitis for 11 and 7 months, have been released from the hospital and 1 has returned to his work as a gasoline station attendant. Seven others, although still hospitalized, are being rehabilitated and are, to all purposes, recovered. The remaining patient, because of active pulmonary tuberculo-

sis which improved during therapy but is still far advanced, remains on a bed-rest regimen. Spinal fluid protein levels remain elevated in 6 of these 10 patients and cell counts are above 10 in 3.

Of the 6 surviving patients whose response has been less dramatic than those of the 10 just described, 1 is still under treatment and it is not fair to evaluate the results of therapy. He appeared moribund when treatment was started and now, after 120 days of therapy, has minimal evidences of active central nervous system tuberculosis.† A 2nd patient, following moderate clinical improvement during therapy, relapsed and is at this time in the end stages of progressive and fatal tuberculous meningitis. Treatment has not been started again. A 3rd patient, experiencing early and marked clinical improvement, continues to have signs of meningitis and further improvement has ceased. The remaining 3 patients, all of them free of active meningeal signs, have active and progressive pulmonary tuberculosis and the final outcome must be considered highly dubious.\*\*

#### Summary of Cases of Meningitis.

Forty-three patients with proven tuberculous meningitis but without evidence of manifest miliary tuberculosis have been treated with streptomycin (Tables 3 and 7). Sixteen died within 6 weeks of onset of therapy without showing any important influence of streptomycin upon the course of their disease. Eleven other patients died, but their life span was definitely prolonged by therapy, 9 of them surviving for an average of 3.3 months and the

other two for 10 and 16 months. Sixteen patients are still alive. Ten of these are free of all signs of infection although, in 6, all constituents of the spinal fluids have not returned to normal values. The remaining patients, although living and improved, continue to show evidences of active tuberculosis and the results of therapy cannot be thoroughly evaluated at the present time. It was found impossible to prognosticate the outcome in any individual case either from the composition of the spinal fluid at the time treatment was started, from the mental status of the patient at that time, or from the interval between the development of symptoms and the initiation of therapy.

#### Laboratory and Clinical Observations and Their Prognostic Significance.

There are collected in Table 8 certain data on the spinal fluid and the clinical status of 68 patients with tuberculous meningitis, both at the time their treatment was started and at its completion. This Table includes all patients in the 2 groups which have been last described and from it are excluded patients whose meningitis did not become manifest until after the institution of treatment for miliary tuberculosis. These data were examined in the hope that certain of them might be of prognostic significance. This hope has not been realized.

Specimens of cerebrospinal fluid (Table 8A), collected prior to treatment, show the anticipated abnormalities in cell count, differential count, protein concentration, and sugar concentration, in the great majority of instances. At the conclusion of treat-

† This patient's therapy was discontinued in November, 1947, following 6 months' continuous treatment with streptomycin. He has made a surprising recovery and is at this time free of central nervous system infection, albeit his spinal fluids continue to be abnormal. This individual remained gravely ill for 3 months despite treatment and significant improvement only began in the 4th month of therapy with streptomycin.

\*\* One of these patients died in November, 1947, from destructive and progressive pulmonary tuberculosis. At the time of death he had been free of all evidences of tuberculous meningitis for more than 7 months and had received no therapy for 4 months.

ment, and to a still greater extent during follow-up observation, the cell count in the surviving patients has been reduced and the sugar concentration returned to its normal range. The protein concentration has been much slower to return to normal, an observation already made by McDermott<sup>7</sup>. No one of these observations provided a constant guide to diagnosis, for the initial sugar concentrations were normal in 22% of the cases and the cell counts and protein concentration normal in 6 and 7% respectively, the diagnosis in these latter instances being made by the demonstration of acid-fast bacilli in the spinal fluid. Nor, in retrospect, could the observations have been used as a prognostic guide. A normal sugar concentration at the pre-treatment observation was no assurance of survival and 4 of the 5 patients with normal protein concentration, and who might thereby have been thought to have a minor infection, died.

The fever and the mental status of the patients (Table 8B) at the time treatment was instituted, was not only markedly alleviated in those who recovered, as has already been remarked, but also in a number of those who did not survive. But neither of these observations proved to be of prognostic import. Several afebrile patients died within a month and others, with very high initial temperatures, proceeded to recovery. Similarly, 2 patients who were initially in deep coma survived, whereas 2 others, who appeared least ill, died rather promptly.

It would seem reasonable to assume that the earlier therapy was instituted the better would be the results. But this assumption was unjustified in this series (Table 8C). In eleven of 43 patients with meningitis, treatment was started within the 1st week of the disease. Five died, 4 within 2 weeks

of the commencement of treatment. Of 12 with disease of more than 2 weeks' duration before the institution of therapy, 6 survived. In those with miliary and meningeal disease, only 1 of 8 survived when treatment was started within 1 week of the onset of the disease, whereas 2 of 5 are still alive, even though therapy was delayed for more than 3 weeks. Moreover, the duration of survival in those who died was not affected by the promptness with which therapy was instituted.

**Toxicity.** Full discussion of the untoward side effects which accompany prolonged administration of streptomycin can be found in the literature<sup>4,7,8,9</sup>. In this series, toxic manifestations were observed in over 95% of the patients, and, excluding for the moment the instances of vestibular hypofunction produced by streptomycin, serious reactions occurred in 28 patients (28%) and hastened death in at least 5 of these (Table 9).

Of the 40 patients still living, deafness or significant hearing loss developed in 7 and a lesser degree of loss occurred in 4 others (28%). The 3 patients (8%) who became completely deaf during treatment have failed to regain their hearing after its termination. The remaining 8 (20%) whose hearing was reduced have regained some degree of hearing and 6 of the 8 are no longer deaf for the conversational range of tones. The loss in hearing usually became manifest by audiometric examination within the 1st month of therapy but did not reach significant degrees until after the 60th day in the majority. From the information thus far available in this series, it is impossible to determine, either clinically or pathologically, whether deafness resulted from the disease or whether it represents a specific streptomycin effect. In the 8

patients whose hearing was not completely lost, 6 did not have equal loss in both ears, one being much worse than the other. This would, by inference, indicate that tuberculosis was the cause of the disability. The very much higher incidence of this complication in the present series (28%) than that which obtains (1.2%) during the treatment of other types of tuberculosis with similar doses of streptomycin<sup>4</sup> argues in the same direction. The examination of pathological specimens of the patients who have died may resolve this argument.

Exfoliative dermatitis occurred in 4 patients. Three of them died shortly after its onset and it was, without doubt, a major contributing cause of death. In all instances, it developed during the 4th week of therapy and had been preceded by a rash and eosinophilia. The 4th patient survived

the exfoliation and is still living. At the time the complication developed, the daily dose of streptomycin was reduced to 1.0 gm. but it was not discontinued as would presumably have been done had the type of tuberculosis been a less fatal one.

Anuria developed in 2 patients and uremia with oliguria in 2 others during the administration of streptomycin. All 4 died but it cannot be stated that streptomycin was the direct cause of death. Two had previously existing renal tuberculosis and the others had evidences of a non-specific nephritis. Diminished function did not become apparent in any of them until after streptomycin had been administered for at least 3 weeks. Pathological examination of kidney tissue did not reveal abnormalities suggestive of a streptomycin effect<sup>7</sup>. Seven patients, without previously known renal dis-

TABLE 8

Clinical and Laboratory Observations In 68 Patients with Tuberculous Meningitis  
With or Without Evidences of Generalized Miliary Tuberculosis

## A. SPINAL FLUID FINDINGS

	Number of Patients			
	Before Therapy (68)	LIVING (21)		DEAD (47)
	Initial Examination	Examination at End of Treatment Period	Last Examination 1 to 9 Months after Cessation of Treatment	Final Examination Before Death
TOTAL NUMBER CELLS/cmm				
Less than 10	4	2	7	3
Between 10 and 50	15	8	5	9
Between 50 and 100	9	1	5	5
Over 100	33	7	2	30
Not reported	7	3	2	0
POLYMORPHONUCLEAR CELLS				
Above 50%	17	1	2	9
Below 50%	42	17	17	35
Not reported	9	3	2	3
PROTEINS				
Normal	5	1	4	0
Between 60 and 100 mg. per 100 cc.	13	6	9	14
Above 100 mg.	44	11	6	29
Not reported	6	3	2	4
SUGAR				
Normal	15	2	6	1
Below normal	31	3	1	24
Not reported	22	16	14	22

TABLE 8 — CONTINUED

## B. CLINICAL FINDINGS

	Number of Patients							
	Before Therapy (68)		LIVING (21)				DEAD (47)	
	Meningitis	Miliary & Meningitis	At End of Treatment	Last Examination	Meningitis	Miliary & Meningitis	Meningitis	Miliary & Meningitis
FEVER								
Below 100 degrees F	5	4	7	4	14	2	3	4
Between 100 and 103° F	20	10	8	1	2	3	8	13
Above 103 degrees F	18	11	1	0	0	0	9	10
MENTAL STATUS								
Clear	9	8	13	4	13	2	3	4
Semi-stuporous	16	8	3	1	3	3	13	9
Deep Coma	18	9	0	0	0	0	4	12

## C. DURATION DISEASE PRIOR TO THERAPY

DURATION AS MEASURED FROM ONSET OF FEVER OR HEADACHE	Number of Patients							
	AT START OF TREATMENT		LIVING (21)		DEAD (47)			
	Meningitis	Miliary & Meningitis	Meningitis	Miliary & Meningitis	WITHIN 6 WEEKS OF THE START OF THERAPY	AFTER MORE THAN 6 WEEKS OF THERAPY	Meningitis	Miliary & Meningitis
1 to 7 days	11	8	6	1	4	3	1	4
8 to 14 days	18	3	3	0	7	3	8	0
15 to 21 days	4	9	2	2	2	6	0	1
Over 21 days	8	5	4	2	2	2	2	1
Unknown	2	0	1	0	1	0	0	0
Total	43	25	16	5	16	14	11	6

TABLE 9

Severe Toxic Manifestations Following Therapy With Streptomycin:  
100 Cases

Reaction	(Number of Patients)	
	Marked or Complete	Minimal or Partial
Hearing Loss	11	9
Kidney Damage	4	7
Exfoliative Dermatitis	4	0
Granulocytopenia	1	1
Total	20	17

Number and Percent of Patients Developing Reactions—29.

ease, developed urinary abnormalities and in 3 of them a mild degree of azotemia appeared. Streptomycin was discontinued in these 3 instances, and kidney function tests and urinalyses reverted to normal shortly thereafter. Streptomycin was continued in the other 4 and although cylindruria, albuminuria, and reduced urea clearance values continued, more serious impairment of kidney function did not develop. Three of the 7 patients died during therapy and specific damage to kidney tissue was not discovered at autopsy. Since cessation of treatment in the remaining 4 patients, the abnormal urinary sediments have cleared, albumin has disappeared from the urine in 3 and urea clearance tests are now normal in all.

Agranulocytosis developed in 1 patient with acute miliary tuberculosis. Because it reached such severe proportions (total count 700), and because angina developed, streptomycin was discontinued. Thereafter, despite progressive and eventually fatal miliary tuberculosis, circulating white blood cell counts returned towards normal. Bone marrow studies were unfortunately not performed. The total white blood cell count in one other patient with meningitis fell to 1500 during therapy but the granulocytes did not disappear completely. Treatment was continued and, despite it, the count returned to normal levels. This patient did not have an associated miliary tuberculosis.

Signs and symptoms of vestibular damage,<sup>2,3,4,6,7</sup> were present in over 90% of all patients who survived more than 6 weeks and have persisted in 37 of the 40 who are still alive.

A complication peculiar to the intrathecal use of streptomycin results from

its irritant action. The great majority of patients receiving streptomycin in doses of 100 mg. or more by this route complained of pain following each injection. The pain appears promptly, is sharp and stabbing in character with a sciatic radiation down both legs which is worse on the dependent side, and may persist with considerable severity for as long as 3 hours. On occasion it has been sufficiently severe so that patients have refused further injections. In addition to the pain, 6 patients have developed paraplegias which were attributed to the local irritant action of streptomycin and were sufficiently marked to require interruption or cessation of intrathecal injections. In each instance, as in Case No. 3, the signs and symptoms disappeared when treatment was discontinued. Further than this, 3 patients have exhibited hyperactive tendon reflexes in both legs for several hours after each of many injections. The incidence of paraplegia appears to be directly related to the size of the intrathecal dose: 3 cases developed in 8 patients receiving daily injections in excess of 100 mg., whereas only 3 developed in 60 cases receiving 100 mg. and none in 60\* receiving 50 mg. every alternate day.

**Summary of Toxicity.** The manifestations of toxicity encountered in this series are not unlike those encountered by other investigators employing similar doses of streptomycin<sup>3,4,8</sup>. Damage to the 8th cranial nerve, to the kidney, and a sensitivity reaction manifested by fever and a skin eruption of varying severity continue to be the most common evidences of toxicity. The most severe reactions and their incidence are listed in Table 9. Three points deserve mention. The effect upon

\* These patients were treated subsequent to May, 1947, and are not included in the present series.

hearing is much more common than has been the case in treating other types of tuberculosis but this may be an indication of disease rather than of toxicity. One case of agranulocytosis and another of leukopenia are reported. Streptomycin is a local irritant and its intrathecal injection produces pain and, on occasion, paraplegia; these phenomena are a function of dosage; they may be minimized, and perhaps abolished, by using slow, well-diluted, injections of 50 mg. of streptomycin on alternate days, a regimen which has been found to maintain adequate concentrations (exceeding 5 micrograms per cc.) in the cerebrospinal fluid.

**Discussion.** One hundred cases of proven acute miliary tuberculosis and tuberculous meningitis have been treated with streptomycin administered by the intramuscular and, in the presence of meningitis, by the intrathecal route. Forty of these patients (Table 3) have had a remission of their disease and survive. Twenty-four patients, who ultimately died, lived for longer than 6 weeks following the institution of therapy and experienced definite clinical improvement during its early stages. These 2 statements provide definite evidence of the usefulness of streptomycin under these circumstances. For the first time, the phthisiologist is armed with an effective chemotherapeutic weapon against diseases which, in all the past, have been uniformly and universally fatal.

This is not to say that the weapon is a perfect one. Sixty percent of the patients are dead and, of the survivors, several have evidence of irreversible brain damage and others, it is anticipated, will suffer relapses and death in their course. The question arises whether the weapon would have given better results had it been differently used, in different dosage or for different lengths of time. The present study

does little to inform on this point for, although there were considerable overall variations in the daily intramuscular (0.6 to 4.0 gm.) and intrathecal (0.01 to 0.2 gm.) dosage, a very large majority of the patients received 1.8 gm. and 0.1 gm. respectively and, of the survivors, a great majority were treated for between 120 and 180 days. Other regimens can therefore scarcely be said to have been explored. At the present time, the effectiveness of larger intramuscular dosage and of administering a combination of streptomycin with intravenous promin is being studied in Veterans Administration hospitals. Insofar as the present series provides evidence on this point, it does not lead one to think that daily doses of less than 1.8 gm. for less than 90 days would be advisable. On the other hand, it seems unlikely that treatment extending beyond 120 days would be useful in a majority of patients since some two-thirds of them will have developed a resistance to streptomycin by this time, if one is willing to accept *in vitro* sensitivity tests as indicative of this state. It is, of course, obvious that a precise definition of dosage can not be given. In those few instances in which clinical improvement continues and in whom organisms remain sensitive to the antibacterial effects of streptomycin, therapy for periods longer than 90 to 120 days is indicated. Indeed it seems important to do so, in order that relapses be prevented. Excluding those instances in which clinical improvement was followed by progression of disease while streptomycin was being administered, a circumstance presumably caused by the development of bacterial resistance, 5 of the 11 relapses in this series occurred after treatment periods of less than 90 days. As the retreatment of 9 of this group of 11 individuals failed to excite a second favorable response, it would

appear that the prevention of a relapse by an adequate first course of therapy is imperative.

It was found that severe reactions accompanied the intrathecal injections of 0.1 gm. or more of streptomycin and it is believed that these reactions can be avoided without comparable loss of efficacy by reducing the dosage to 0.05 gm. and injecting it slowly and well diluted. As was pointed out in the preceding section, injections of 50 mg. on alternate days will maintain presumably effective spinal fluid concentrations of streptomycin for the 48-hour interval. It appears from this series that every-other-day injections for 3 or 4 months will provide adequate intrathecal therapy for tuberculous meningitis and that this total number (40 to 50) will be tolerated by most patients. Although the comparable effectiveness of intramuscular versus intrathecal streptomycin in the treatment of tuberculous meningitis would be interesting to determine, a study of this character has not appeared justifiable.

In the body of this article, the diseases with which it is concerned have been described separately and in the several combinations in which they occurred. By all odds the most successful results have occurred in the patients with acute miliary disease unaccompanied by meningitis. Of the 22 cases in this group, 16 (73%) are alive for from 4 to 14.5 months following the initiation of therapy and 14 have apparently recovered. Roentgenographic evidence of pulmonary dissemination, in these patients, has commenced to clear after 60 days of treatment and has frequently gone on to complete disappearance. This is quite consistent with the demonstration<sup>2</sup> that recent, small, pulmonary lesions respond best to streptomycin, but it is, nevertheless, a quite novel and dramatic observation.

On the other hand, the group which has responded least well to streptomycin has been composed of patients with both meningeal and disseminated tuberculosis. Although 5 of these (20%) are still alive, only 2 are free of evidence of nervous system and pulmonary infection and 1 of these 2 has irreversible brain damage. One can only speculate as to the reason for the failure. It is consistent with the unfortunate association of the two diseases that, of 10 patients who developed meningitis either during or subsequent to treatment of their miliary tuberculosis with streptomycin, only 3 are living 9 to 12 months after the onset of their disease and but 1 of these 3 could be characterized as a recovery. The development of meningitis has come to appear as the chief obstacle to the successful treatment of miliary disease by streptomycin. These findings do not vitiate the previous statements concerning the effectiveness of streptomycin upon pulmonary disseminations for, in a majority of the patients who lived sufficiently long, a definite clearing of these lesions was observed antecedent to death. In the 3 instances of combined disease in which improvement occurred and was maintained, the remission of the infections in each might be explained by the antimicrobial effect of streptomycin which was accompanied and followed by a sufficient response of the host's defense and reparative mechanisms. Thus control of the infection developed and the remission became sustained. On the other hand when improvement of the infection was not maintained, one can speculate that at the time the host's organisms became resistant to the antibacterial effect of streptomycin, improvement ceased and relapse occurred because the host was unable to produce adequate defenses. In the group who did not respond to



any degree and in those who developed central nervous system residua, the failure of streptomycin may be attributable to its inability to promote beneficial changes in established irreversible pathological situations.

Falling midway between these 2 groups, from the point of view of results, are the 43 patients with tuberculous meningitis unaccompanied by other evidence of a disseminated process. Sixteen of these patients (37%) are living 4 to 7 months after the beginning of treatment and, although the cerebrospinal fluid has become completely normal in only 4, 10 of them have completely recovered from all clinical evidence of disease. This is, of course, quite without precedent, and must be attributed solely to streptomycin, even though it be admitted that some, or even all, of these patients may subsequently suffer relapses and death. Because the permanence of the clinical remissions can not be predicted, the term "cure" has been purposely avoided throughout.

**Summary.** One hundred patients with proven acute miliary tuberculosis and/or tuberculous meningitis have been treated with streptomycin in 52 Veterans Administration and contract hospitals. Forty of these patients are still alive between 4 and 14.3 months following the initiation of treatment. The pulmonary dissemination of miliary tuberculosis proved the most responsive to streptomycin but a considerable number (37%) of patients with tuberculous meningitis have also survived.

These results are interpreted not so much as meaning that streptomycin can cure these 2 types of disease but rather as indicating, beyond cavil, that it is capable of influencing favorably the course of tuberculosis.

**Addendum:** It is proposed to publish

in this Journal, at intervals, a brief note describing the fate of the 40 survivors of the group. The first of these notes is as follows:—

On June 1, 1948, 8 months after this report had been submitted for publication, 24 of the 100 patients were alive. Fifteen of the 40 survivors described had died and one was lost to the follow-up.

Three of the deaths during the past 8 months occurred in the group originally with miliary tuberculosis. All developed meningitis. Seven individuals with meningitis died, 5 during relapse or progression of the original disease and 2 following progressive pulmonary disease. Neither of these latter had evidences of meningeal tuberculosis at the time of death. Five patients who had combined miliary and meningeal tuberculosis died, all with recurrences or progression of the original meningitis. Three of these latter 5 had no pulmonary miliary involvement at autopsy.

Of the 24 patients still living, 10 have moderate to severe impairment of labyrinthine function, 1 continues deaf and 3 have neurologic sequelae, either from central nervous system damage or from the irritant effects of intrathecally-administered streptomycin.

Eight patients have foci of tuberculosis, other than the disseminated form, which are still active. Only 1 patient, whose miliary dissemination was followed by meningitis, is living and he is undergoing a fourth course of treatment for meningeal relapse. Although the miliary lesions remain "cured," his prognosis is grave.

Fifteen patients are either free of tuberculosis or have arrested lesions; 7 were treated originally for miliary tuberculosis, 7 for meningeal disease, and 1 had therapy for combined disease.

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# AN EVALUATION OF THE THYMOL TURBIDITY TEST

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The original observation by MacLagan<sup>1</sup> in 1944 on the thymol turbidity test as a measure of liver dysfunction has received extensive investigation by Watson and Rappaport,<sup>13</sup> McCord, Kline and Williams,<sup>7</sup> Shank and Hoagland,<sup>12</sup> Mateer *et al.*,<sup>5,6</sup> and Neefe.<sup>8</sup> The modification of MacLagan's original technique recommended by Shank and Hoagland<sup>12</sup> has not been widely used, although it represents an improvement in the sensitivity of the test and the objectiveness of the results. Our interest in the test was stimulated by the ease and speed with which it is accomplished in the laboratory. Accordingly the present investigation was undertaken:

1. to determine the desirability of adopting the thymol turbidity test as a routine laboratory procedure.
2. to investigate some of the factors which may alter the results of the test.
3. to establish the results of the thymol turbidity test in a large series of persons who on routine physical and laboratory examination appear normal.
4. to determine the results of the thymol turbidity test when run on a large series of hospital admissions with diseases generally believed not to involve the liver.
5. to add to the reports already in the literature the results of the thymol turbidity test in patients with various kinds of liver disease.

6. to compare the results of this test with the cephalin cholesterol flocculation test of Hanger.<sup>10</sup>

**Method and Procedure.** The cephalin cholesterol flocculation test was performed as described by Hanger<sup>10</sup> with the modification introduced by Neefe and Rheinhold.<sup>9</sup>

The thymol-barbital buffer of pH 7.8 was prepared as described by MacLagan.<sup>4</sup>

The tests were performed by adding 0.1 cc. of serum to 6.0 cc. of the thymol barbital buffer in a calibrated test tube which was stoppered, shaken, and allowed to stand for 30 minutes. At the end of that time the tubes were inverted once and read in a Klett-Summerson photoelectric colorimeter equipped with a red filter of light transmission limits of 640 to 700  $m\mu$  with maximum transmission at 660  $m\mu$ . The galvanometer was adjusted to 100% transmission of light with a blank containing 6.0 cc. of thymol buffer. The turbidity of a given reaction is expressed in units derived from a standard curve prepared by using barium sulfate suspensions as recommended by Shank and Hoagland.<sup>12</sup> The quantities of standards prepared were double those used by these authors in order to adapt the procedure to the Klett-Summerson photoelectric colorimeter. If a test tube containing 6.0 cc. of distilled water is used as a blank, there is a straight line relationship between the optical densities of various dilutions of the barium sulfate standard at 660  $m\mu$ . This relationship was found to be true for a wave length of 650  $m\mu$  by Shank and Hoagland. Since the start of the present investigation Dodds<sup>2</sup> has used a modification of the Shank and Hoagland procedure which is identical with that used in this paper.

**Material.** The subjects for these tests were patients on the surgical and medical wards of St. Luke's Hospital. Specimens of blood for normal controls were obtained from the resident population of the hospital and from donors to the blood bank. All subjects except the blood bank donors had a complete physical examination including urinalysis, blood Wassermann, and chest roentgenograms. The blood bank donors had a superficial physical examination and blood hemoglobin determination. Donors with a history of jaundice were not used. Patients with suspected liver damage or those whose sera gave elevated readings of thymol turbidity were investigated more completely.

**Results.** A. While the procedure for determining the thymol turbidity of sera was being established, it was deemed advisable to test certain factors which might influence or change the results of the test. Three such

fast was 3.0 units, after breakfast 3.1 units, and after lunch 3.6 units. Six patients with high thymol turbidity readings gave an average reading before breakfast of 8.3 units, after breakfast 9.0 units, and after lunch 9.7 units. Apparently the thymol turbidity test is not greatly influenced by the intake of food, although there seems to be a slight rise after meals. This series is too small to justify any quantitative conclusions, but it is recommended that all specimens be taken on a fasting stomach if possible.

3. McCord *et al.*,<sup>7</sup> used sera for the thymol turbidity test which had been previously inactivated for the Wassermann reaction. The effect of inactivation by heating at 56° C. for 30 minutes was therefore tried on a number of sera to see if such sera could be made available for the thymol turbidity test.

TABLE 1. EFFECT OF REFRIGERATION ON THYMOL TURBIDITY VALUES

	<u>Days of Refrigeration</u>							
	0	1	2	3	4	5	7	14
Normal Thymol Turbidity Values.....	2.6	3.3	3.0	3.2	2.1	1.8	2.2	2.1
(Average of 9 cases)								
Elevated Thymol Turbidity Values.....	13.6	14.4	14.2	13.8	13.5	13.7	13.6	13.5
(Average of 6 cases)								

factors were investigated.

1. Standing at a temperature of 10° C. seemed to have little effect on the readings of 9 normal sera and 6 sera with elevated readings. The results are shown in Table 1 and show a rather remarkable degree of constancy over a 2-week period. It would seem, therefore, that thymol turbidity tests on refrigerated sera will be accurate over considerable periods of time. This might find application in the testing of blood bank blood or plasma.

2. The effect of the time of day when the sample of blood is drawn was then studied. Specimens were obtained before breakfast, after breakfast, and after lunch. The average reading for 7 normals before break-

On 54 sera the thymol turbidity readings before inactivation gave an average figure of 6.4 units; after inactivation, 3.9 units. From these results it was concluded that inactivation lowers the thymol turbidity readings sufficiently to make them inaccurate. It was felt that the low results obtained by McCord and his coworkers were probably due to this effect of inactivation.

4. The effect of inactivation on the cephalin-cholesterol flocculation test was also investigated. Sera which gave negative cephalin-cholesterol flocculation tests were inactivated as described above and then tested again; all showed a change from negative to 2+ or more. These results show that the Hanger test cannot be run on inacti-

vated sera. Furthermore, the fact that one test becomes positive (Hanger) and the other negative (thymol turbidity) would seem to be evidence of the essential chemical difference between these two tests and that they depend upon different components of the serum. This is in agreement with the conclusions of Recant, Chargoff, and Hanger<sup>11</sup> and others.<sup>1,6,13</sup>

B. *Normals*. 552 observations on 500 supposedly normal individuals were made. Where more than one deter-

Figure 1, however, that a considerable number of normals have readings above 5.0 in our series, in fact, 13%. An analysis of these results leads to some interesting conclusions:

1. A number of normals with elevated thymol turbidity readings were tested again after varying time intervals. These repeated readings are tabulated in Table 2. Repeat tests on a series of normals with low thymol turbidity readings were also made. The results are tabulated in Table 2a. The

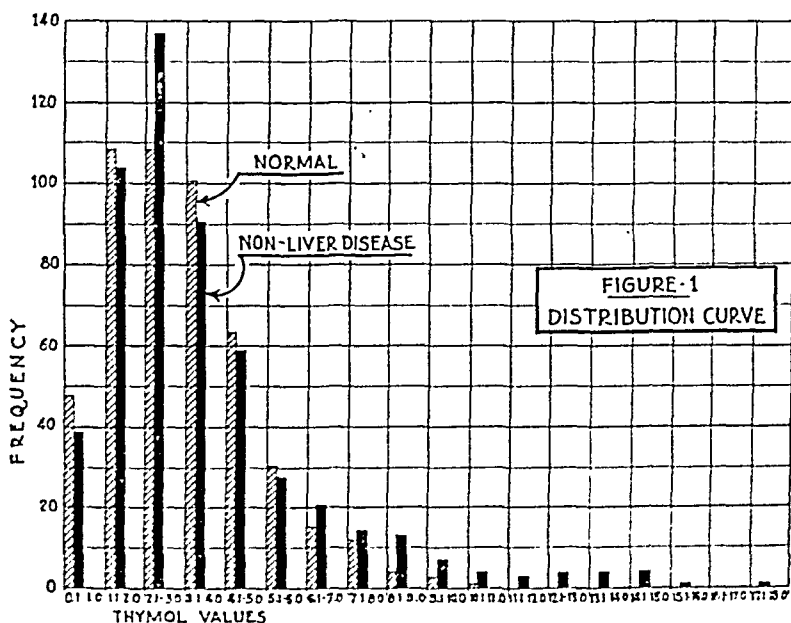


FIG. 1.—Distribution of thymol values in 500 normal persons.

mination was made on a subject the average of these was taken as the figure for that person. The mean value was 3.2 with a mean deviation of 1.8. Figure 1 shows the distribution of the results obtained on these 500 normals. Shank and Hoagland,<sup>12</sup> using barium sulfate standards and a spectrophotometer, obtained no readings above 5 units in 46 normal subjects. Similar normal values have been reported more recently by other observers.<sup>2</sup> It will be seen from inspection of

constancy of the readings is apparent. All these subjects were in apparent good health and going about their usual daily work. It would seem therefore that a certain per cent of normal people do run a constantly elevated thymol turbidity test.

2. From the theory of probabilities, about two-thirds of all observations in an experimental series should not be farther from the mean than  $\pm r$ , where  $r$  is equal to the mean deviation for the series. Applying this theory, we

TABLE 2. REPEATED DETERMINATIONS ON ELEVATED THYMOL TURBIDITY READINGS (NORMAL CASES)

<i>Initial Reading</i>	<i>Repeat #1</i>	<i>Repeat #2</i>
6.0	4.8	4.4
5.8	4.4	
6.5	5.5	
7.4	5.1	
5.7	6.2	
7.0	8.2	8.2
8.2	10.3	
8.0	4.7	
5.3	6.5	
10.2	11.5	
6.5	6.6	
7.0	7.7	7.4
5.1	5.8	
8.2	8.2	
5.1	7.5	
5.3	7.3	
6.4	6.9	
6.9	6.7	
4.8	5.7	4.8
5.5	3.7	
5.5	4.7	

TABLE 2A. REPEATED DETERMINATIONS ON READINGS BELOW 5.0 UNITS OF THYMOL TURBIDITY

<i>Initial Reading</i>	<i>Repeat #1</i>	#2	#3	#4	#5	#6	#7	#8	#9
2.3	1.1	1.9							
0.2	1.7								
2.3	3.0								
3.0	2.0								
4.0	4.5	3.6	4.0	3.5					
1.8	2.7								
1.4	1.7								
4.0	3.8								
3.6	2.3	2.5	2.6	2.9	2.3	2.7	1.9	3.0	1.3
3.6	4.8								
3.2	4.0								
3.0	2.6								
2.3	4.1								
4.7	4.8	2.9	4.1						

find that 66% of our normals fall in the range of 1.4 to 5.0 units which is  $3.2$  (the mean)  $\pm 1.8$  (the mean deviation). 95% of the normals lie in the range from 0.0 to 6.8 units (mean  $\pm 2\epsilon$ ) and 99% lie in the range of 0.0 to 8.6 units (mean  $\pm 3\epsilon$ ), which again complies with the theory of probabilities. It appears then that (a) one would not expect all normals (in a large enough series) to be as close to the mean as previous investigators have reported, and (b) that it is to be expected to find a certain number of normal persons

with readings even as high as 9.0 units.

3. Eighty-seven percent of our normals lie within the 0.0 to 5.0 unit range. It can probably be concluded, therefore, that the normal range is usually 0.0 to 5.00. Eighty-seven percent accuracy is probably as perfect as one can expect most biological tests to be. It must be borne in mind, however, that there are a certain number of normal individuals whose thymol turbidity readings will lie above this range and that without clinical and other supporting laboratory evi-

dence it must not be concluded that they have liver disease.

*C. Diseases not involving the liver.* There were 538 observations on 527 patients admitted to the hospital and diagnosed as having disease not commonly considered to involve the liver. Again where more than one determination was made on a subject the average of these was taken as the reading for that individual. The mean value of this series was 3.7 with a mean deviation of 2.7. Figure 1 shows the distribution of the results obtained on these 527 hospital admissions and compares them graphically with the distribution of the normals.

Several important facts should be noted:

1. The mean for this series closely approximates the mean for the normals.

2. The curves for the 2 series are similar in contour, there being a slight shift to the right (higher units) in the patients with disease other than liver disease. This shift is probably caused by the inclusion, in the second series, of patients with diseases which in some cases gave elevated readings during the acute phase (cf. Table 3).

3. Again subjecting these results to the theory of probabilities, it is apparent that they also conform to what might be expected, in that 66% are in the range from 1.0 to 6.4 units of thymol turbidity ( $3.7 \pm 2.7$ ), 95% within the range of 0.0 to 9.1 units ( $3.7 \pm 5.4$ ), and 99% within the range of 0.0 to 11.8 units ( $3.7 \pm 8.1$ ).

4. If we assume again that the normal range is from 0.0 to 5.0 units, we find from Figure 1 that 20% of hospital patients with disease other than liver disease will run an elevated thymol turbidity test. It would appear, therefore, that the thymol turbidity test can be used on routine hospital admissions with disease other than liver disease with an expected accuracy of

80% if we assume that all persons except those with liver disease should have readings below 5.0 units. 20% of such admissions will show elevated readings for unknown reasons.

In all, the thymol turbidity test was tried on more than 100 different disease entities. Of these, 61 gave readings within the accepted normal range of 0.0 to 5.0 units, and 39 gave one or more positive values. Where there was more than one reading for a case, the average of the readings was taken and is shown in Table 3. It is interesting to note the high incidence of positive readings in patients with secondary syphilis, infectious mononucleosis, sickle cell anemia in crisis, malaria, and virus pneumonia. It would appear also that patients with cardiac decompensation also have a higher incidence of positive readings than those who are compensated.

Forty-one cases with many different kinds of neoplasms, with and without metastases, were examined. Nine of these showed some elevation (5.1 to 12.7). The highest of these were observed in patients with extrahepatic biliary obstruction of long standing due to carcinoma of the common duct, ampulla of Vater, or metastatic carcinoma in the porta hepatis. However, several cases of carcinoma of the stomach with extensive metastases to the liver demonstrated at autopsy were repeatedly tested and showed no elevation of thymol turbidity or only a rise of one point just prior to death. The test is therefore of no value in detecting the presence of liver metastases.

The diseases in which no positive readings were obtained are listed in Table 4. In most of these only one or two patients per disease were examined so that the possibility of some positive results in these diseases, given a large enough series of each, must be entertained.

TABLE 3. SUMMARY OF RESULTS OF PATIENTS WITH DISEASE NOT COMMONLY REGARDED AS INVOLVING THE LIVER, BUT WHOSE SERA GAVE ELEVATED THYMOL TURBIDITY VALUES

<i>Disease</i>	<i>Total Cases</i>	<i>Positive Cases</i>	<i>Readings of Individual Positive Cases*</i>				
Anemia.....	5	1	(9.6) <sub>2</sub>				
Osteomyelitis.....	1	1	(8.7) <sub>4</sub>				
Subdeltoid Bursitis.....	1	1	6.4				
Thrombocytopenic Purpura.....	2	1	(12.9) <sub>3</sub>				
Perirectal Abscess.....	1	1	10.7				
Lupus Erythematosus.....	2	1	(8.1) <sub>2</sub>				
Amoebic Colitis.....	2	1	5.5				
Intestinal Obstruction.....	2	1	(6.6) <sub>2</sub>				
Pilonidal Cyst & Sinus.....	2	1	5.7				
Malaria in Crisis.....	2	2	14.3	(14.0) <sub>2</sub>			
Paroxysmal Nocturnal Hemoglobinuria.....	1	1	(7.6) <sub>6</sub>				
Arteriosclerotic Heart Disease with Decompensation.....	17	5	(7.8) <sub>6</sub>	(5.1) <sub>3</sub>	10.9	6.2	7.8
Rheumatic Heart Disease with Decompensation.....	14	3	(8.0) <sub>7</sub>	(11.9) <sub>4</sub>	(7.8) <sub>4</sub>		
Rheumatic Heart Disease without Decompensation.....	5	2	6.6	(8.1) <sub>2</sub>			
Coronary Occlusion.....	18	4	6.5	7.0	5.5	6.6	
Arteriosclerosis.....	9	4	5.8	12.3	7.7	8.2	
Hypertensive Cardiovascular Disease Decompensated.....	13	4	(11.7) <sub>3</sub>	(13.1) <sub>3</sub>	(5.8) <sub>3</sub>	(6.0) <sub>2</sub>	
Hypertensive Cardiovascular Disease not Decompensated...	11	3	(8.2) <sub>2</sub>	5.4	(6.2) <sub>3</sub>		
Late Latent Syphilis.....	33	9	9.3 14.9	(9.1) <sub>2</sub> 13.3	9.0 8.7	(7.9) <sub>2</sub> (5.6) <sub>3</sub>	(14.9) <sub>2</sub>
Secondary Syphilis.....	9	7	5.4 5.1	(5.7) <sub>2</sub> 7.8	6.7	(7.6) <sub>6</sub>	12.7
Central Nervous System Syphilis	28	4	5.8	(6.5) <sub>2</sub>	(5.7) <sub>3</sub>	(7.8) <sub>7</sub>	
Neoplastic Diseases with & without Metastases.....	41	9	5.1 6.9	7.3 5.5	5.3 9.3	6.0 (6.7) <sub>5</sub>	6.6
Acute & Chronic Alcoholics.....	17	3	(9.5) <sub>2</sub>	(7.0) <sub>2</sub>	5.4		
Infectious Mononucleosis.....	9	8	12.4 7.2	7.4 11.2	15.6 13.2	8.4 13.9	
Acute Active Rheumatic Fever.	3	1	(9.6) <sub>11</sub>				
Virus Pneumonia.....	3	3	5.8	(6.7) <sub>2</sub>	(5.7) <sub>6</sub>		
Sickle Cell Anemia in Crisis.....	3	2	(11.0) <sub>3</sub>	(6.1) <sub>4</sub>			
Tuberculosis, Pulmonary and Elsewhere.....	10	3	(5.2) <sub>2</sub>	5.4	(8.3) <sub>4</sub>		



TABLE 3.—(Continued)

<i>Disease</i>	<i>Total Cases</i>	<i>Positive Cases</i>	<i>Readings of Individual Positive Cases*</i>				
Chronic and Acute Otitis Media.	4	1	6.6				
Diabetes Mellitus . . . . .	17	2	(6.0) <sub>2</sub>	(5.4) <sub>2</sub>			
Arthritis . . . . .	20	5	5.1	5.8	10.3	10.9	12.6
Thrombophlebitis . . . . .	3	1	(8.1) <sub>2</sub>				
Diseases of the Female Genital Tract . . . . .	14	2	(5.2) <sub>2</sub>	5.1			
Upper Respiratory Infection . . . .	11	2	(5.1) <sub>2</sub>	(12.6) <sub>2</sub>			
Neuropsychiatric Disorders . . . .	10	4	7.4	(6.5) <sub>2</sub>	(5.7) <sub>4</sub>	6.7	
Fractures . . . . .	7	1	(9.4) <sub>4</sub>				
Gastroenteritis . . . . .	19	2	(5.7) <sub>2</sub>	(5.4) <sub>2</sub>			
Pneumococcus Pneumonia . . . . .	11	3	(6.7) <sub>2</sub>	(6.2) <sub>2</sub>	(17.2) <sub>2</sub>		
Multiple Sclerosis . . . . .	1	1	(6.4) <sub>2</sub>				
Peptic Ulcer With & Without Gastric Resection or other Operation . . . . .	10	1	(8.6) <sub>4</sub>				

\* Sub-letter indicates number of determinations on a case.

TABLE 4. SUMMARY OF RESULTS OF PATIENTS WITH DISEASE NOT COMMONLY REGARDED AS INVOLVING THE LIVER, AND WHOSE SERA GAVE NORMAL THYMOL TURBIDITY VALUES

<i>Disease</i>	<i>Total Cases</i>	<i>Disease</i>	<i>Total Cases</i>
Myelodysplasia . . . . .	2	Congenital Syphilis . . . . .	2
Sydenham's Chorea . . . . .	1	Hernia . . . . .	7
Myositis . . . . .	1	Various Avitaminoses . . . . .	8
Keratitis . . . . .	1	Various Kidney Diseases (except neoplasms) . . . . .	12
Allergic Rhinitis . . . . .	2	Urinary Tract Diseases . . . . .	5
Varicose Veins with and without Ulcer . . . . .	3	Rickettsial Diseases . . . . .	5
Subluxation of Shoulder . . . . .	1	Thyrotoxicosis . . . . .	6
Exostoses of Feet . . . . .	1	Acute and Chronic Sinusitis . . . . .	6
Intercostal Neuralgia . . . . .	1	Diverticulitis and Diverticulosis . . . . .	4
Post-vaccination Encephalitis . . . . .	1	Phlebotomiasis . . . . .	1
Jacksonian Epilepsy . . . . .	1	Chronic Pancreatitis . . . . .	1
Cerebellar Ataxia . . . . .	1	Gastric Hiatus Hernia . . . . .	1
Generalized Osteoporosis of Spine . . . . .	1	Non-specific Colitis . . . . .	2
Acute Gout . . . . .	1	Herniated Nucleus Pulposus . . . . .	1
Schistosomiasis . . . . .	1	Hypothyroidism . . . . .	1
Hemorrhoids . . . . .	3	Hemolytic Jaundice . . . . .	2
Gynecomastia . . . . .	1	Hypoproteinemia . . . . .	1
Laceration of Scalp . . . . .	1	Elephantiasis (filariasis) . . . . .	1
Leukopenia . . . . .	1	Enlarged Thymus Gland . . . . .	1
Achylasia of Oesophagus . . . . .	1	1st & 2nd Degree Burns . . . . .	1
Constrictive Calcific Pericarditis . . . . .	1	Vincent's Gingivitis . . . . .	1
Congenital Heart Disease . . . . .	2	Appendicitis . . . . .	3
Arteriosclerotic Heart Disease not Decompensated . . . . .	9	Chronic Bronchitis } . . . . .	6
Abnormal Rhythm of Heart . . . . .	1	Bronchiectasis } . . . . .	
Essential Hypertension . . . . .	7	Bronchial Asthma } . . . . .	
		Early Latent Syphilis . . . . .	1
		Primary Syphilis . . . . .	5
		Dermatitis of Various Kinds . . . . .	12

D. *Liver disease.* The results of the thymol turbidity test in the presence of liver disease are presented in Table 5. It is in these diseases, especially the cases of infectious hepatitis, that the test is most useful. Of 37 patients with infectious hepatitis, all showed some degree of elevation of the thymol turbidity. The test reaches its maximum at about the time of maximum morbidity and just prior to the development of maximum icterus. Figure 2 represents graphically the

course of the disease as it is usually portrayed with serial determinations of the thymol turbidity test. This is a composite curve derived by averaging the readings of 12 cases at comparable intervals along an 80-day follow-up. It will be seen that the test yields maximum readings on about the 10th hospital day, which is usually about the 14th day of illness. In this disease the thymol turbidity remains elevated for long periods. In severe cases one frequently finds the test considerably

TABLE 5. SUMMARY OF LIVER CASES

Condition	Number of Cases	Number of Positive Cases	Summary of Positive Cases		
			Average	Highest Single Observation	Lowest Single Observation
Homologous Serum Jaundice.....	1	1	5.4	8.0	2.7
Congenital Atresia of Bile Duct.....	1	1	22.1	26.5	17.6
Toxic Hepatitis.....	4	2	6.9	10.0	3.6
Parasitic Infection of Liver.....	3	1	7.1	8.6	5.1
Biliary Dyskinesia.....	4	0			
Carcinoma of Liver, Primary or Meta- static, Without Jaundice.....	3	1	5.1	7.0	3.0
Carcinoma of Liver, Primary or Meta- static, With Jaundice.....	5	2	15.0	25.4	6.0
Sub-hepatic Abscess.....	2	2	8.7	15.6	3.8
Chronic Cholecystitis With Cholelithia- sis, With Jaundice.....	8	6	11.1	24.2	3.2
Chronic Cholecystitis, With Cholelithia- sis, Without Jaundice.....	18	1	6.7		
Chronic Hepatitis.....	7	7	9.2	16.5	5.1
Cirrhosis.....	31	22	10.3	21.1	5.1
Infectious Hepatitis.....	37	37	17.4	33.1	7.3

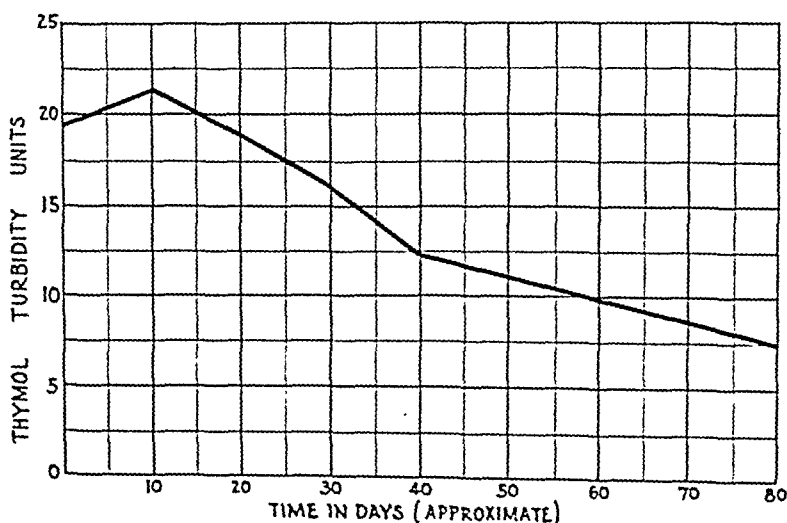


FIG. 2.—Thymol turbidity time curve. Average 12 cases.

elevated (15 units) one month after the diagnosis has been made and slightly elevated for from 3 to 9 months thereafter. The test does not correlate very well with the disappearance of jaundice and the improvement in the patient's subjective findings. The jaundice may have disappeared and the patient may feel quite well while the thymol turbidity test is still elevated. This might mean (a) that the test is not a true measure of the function of the liver, or (b) that it is a very sensitive indicator of persisting liver damage. Experience of other workers<sup>5</sup> who found residual inflammatory tissue in the periportal region in serial biopsies taken over a period of months following infectious hepatitis would indicate that the second interpretation above is probably correct.

may be an indication of the severity of the individual case.

The diagnosis of Laennec's cirrhosis is frequently a difficult one. MacLagan<sup>4</sup> originally reported 13 positive thymol turbidity tests in 13 cases of cirrhosis with an average reading of 14.2 units and with a variation of  $\pm 2.0$  units. On the basis of this report, it was hoped that we could demonstrate the usefulness of this test in a similar series. However, in 31 cases of cirrhosis of the liver, only 22 showed positive determinations. The readings ranged from 0.6 to 21.1 units. That our results were at variance with reports of other workers became apparent early in the course of this investigation. Cases of cirrhosis were, therefore, selected in which the diagnosis was substantiated by autopsy, biopsy, peritone-

TABLE 6. COMPARISON OF THYMOL TURBIDITY AND CEPHALIN-CHOLESTEROL FLOCCULATION TESTS

Cephalin-Cholesterol Flocculation Test	—	+-	1+	2+	3+	4+	Total Cases	Percent
Thymol Turbidity (0.1-5.0 Units) . . .	172	43	23	21	18	2	235	78.4
Thymol Turbidity (5.1-11.5 Units) . .	20	9	6	6	4	5	73	21.6
Total Tests . . . . .	201	52	29	27	22	7	338	100.0
Percent . . . . .	59.5	15.4	8.6	8.0	6.5	2.0	100.0	

Perhaps one good feature of the thymol turbidity test is the fact that it is graded in numerical units ranging over a wide scale. Thus, a patient with an initial reading of 15 units who subsequently has readings of, for example, 18, 20, 23, 27 may be said to be getting worse. During recovery, the thymol turbidity can be seen to fall toward normal as, for example, from a high of 26 to 21, 20, 15, 12, 10, 7, 5, etc. This gives a precise and graphic picture of recovery. The long period of time during which positive thymol turbidity tests are obtained is probably evidence of the chronicity of infectious hepatitis. The degree of elevation of the test during the acute phase of the disease

oscopy, or prolonged observation with repeated laboratory tests. No correlation between the degree of periportal fibrous tissue deposition and the degree of elevation of the thymol turbidity test could be obtained. Some additional factor superimposed upon the cirrhosis, such as cardiac failure, acute hepatitis (toxic or infectious), porto-caval shunt, or uncontrolled diabetes mellitus was usually present in the cases in which the readings were elevated. It would appear, then, that "compensated" cirrhotics in which there is considerable periportal fibrosis with abdominal ascites, but in whom the remaining liver parenchyma is functioning adequately for body needs, do

not show an elevation of thymol turbidity. When, however, these remaining parenchymal cells are damaged by an infection or by a toxin (alcohol, sulfadiazine) or by anoxia (cardiac decompensation), then the thymol turbidity test becomes positive and measures the degree of dysfunction of the remaining parenchyma. A return of the test to normal readings indicates a return of the cirrhotic to the "compensated" state. However, since the disease is frequently accompanied by a chronic hepatitis due to alcohol or other deleterious agent, the thymol turbidity readings sometimes remain constantly elevated (6.0 to 12.0 units).

One case of homologous serum jaundice gave elevated readings during the icteric phase of the disease, which returned rapidly to normal with the disappearance of the jaundice. Seven cases of chronic hepatitis all showed elevated thymol turbidity tests ranging from 5.1 to 16.5 units. These cases were classified as chronic hepatitis because of the duration of symptoms and signs for more than 3 months and because there was no history of antecedent infectious hepatitis. Three cases of toxic hepatitis due to chemical poisons and one due to pneumococcus toxin showed elevated readings. These diseases may be grouped with decompensated cirrhosis and infectious hepatitis as examples of parenchymatous liver disease, the degree of which is adequately measured by the thymol turbidity test.

Of 3 cases of parasitic infestation of the liver, only the one with amoebic hepatitis gave positive findings. One case with *schistosoma mansoni* and one with liver flukes gave normal findings.

Metastatic carcinoma of the liver has been discussed above. Primary carcinoma of the liver also gave equivocal results. Where the tumor had involved the biliary tract to cause long-standing

obstruction to the outflow of bile, the readings were usually elevated. A similar case of long-standing obstruction in an infant with congenital atresia of the bile ducts showed marked and persistent elevations. Where there was no obstructive jaundice the extent of replacement of normal liver parenchyma could not be correlated with elevated thymol turbidity readings.

Two cases of subhepatic abscess with jaundice and penetration into the liver gave positive tests. These were both secondary to duodenal ulcer and associated with generalized peritonitis.

Four cases of biliary dyskinesia all had normal values.

Of 8 cases of chronic cholecystitis with cholelithiasis and jaundice, 6 gave thymol turbidity readings varying from 3.2 to 24.2 units, whereas 18 similar cases without jaundice gave only one positive test (6.7 units). The diagnosis in these cases of cholecystitis with cholelithiasis was substantiated either at operation or by cholecystograms. The presence or absence of biliary obstruction again seemed to be an important factor in the production of elevated thymol turbidity readings. The longer it persisted, the more marked the elevation.

In order to compare the thymol turbidity test with a standard test of liver function used widely in hospital laboratories, the cephalin-cholesterol flocculation test was determined on as many of the persons tested with the thymol turbidity test as possible. There were 338 such determinations on 308 apparently normal individuals. For the same series there were 235 thymol turbidity determinations with readings of 5.0 units or below, and 73 with readings ranging from 5.0 to 11.5 units. These results are summarized in Table 7. Examination of this table reveals that 21.6% of apparently normal individuals will show a somewhat ele-

TABLE 7. PATIENTS WITHOUT LIVER DISEASE. COMPARISON OF THYMOL TURBIDITY AND CEPHALIN-CHOLESTEROL FLOCCULATION TESTS

Cephalin-Cholesterol Flocculation Test.	—	+-	1+	2+	3+	4+	Total	Percent
Thymol Turbidity (0.1-5.0 Units)...	328	44	72	76	54	29	603	71.0
Thymol Turbidity (5.1-21.8 Units)...	65	16	22	38	54	55	245	29.0
Totals.....	393	60	94	109	108	84	848	100.0
Percent.....	46.3	7.1	11.1	13.0	12.7	9.9	100.0	

TABLE 8. PATIENTS WITH LIVER DISEASE. COMPARISON OF THYMOL TURBIDITY AND CEPHALIN-CHOLESTEROL FLOCCULATION TESTS

Cephalin-Cholesterol Flocculation Test.	—	+-	1+	2+	3+	4+	Total	Percent
Thymol Turbidity (0.1-5.0 Units)...	61	3	8	10	15	11	117	24.5
Thymol Turbidity (5.1-38.6 Units)...	30	10	19	42	91	168	360	75.5
Totals.....	91	13	27	61	106	179	477	100.0
Percent.....	19.1	2.7	5.7	12.8	22.2	37.5	100.0	

TABLE 9. COMPARISON OF THYMOL TURBIDITY AND CEPHALIN FLOCCULATION TESTS IN PATIENTS HAVING LIVER DISEASE WITH AND WITHOUT ICTERUS

	ELEVATED ICTERIC INDEX						NORMAL ICTERIC INDEX					
	Obstruction 13 observations on 16 cases			No obstruction 293 observations on 61 cases			Obstruction 13 observations on 9 cases			No obstruction 94 observations on 37 cases		
	Neg.	Pos.	3+, 4+	Neg.	Pos.	3+, 4+	Neg.	Pos.	3+, 4+	Neg.	Pos.	3+, 4+
Hanger Determinations	11	33	27	26	266	208	10	9	1	35	59	37
Percent	25	75	61	9	91	71	77	23	8	37	63	59
Thymol Turbidity Determinations	0	0-5	6	5	1 & Up		0	0-5	0	5	1 & Up	
	15		29	34		259	11		2	31		43
Percent	34		66	12		88	84		16	66		54

vated thymol turbidity test. As we have seen previously, the theory of probabilities would lead us to expect at least this per cent of normals to show elevated readings. Similarly, if we assume that any degree of flocculation above plus or minus, which is an equivocal reading, is a positive cephalin cholesterol flocculation test, we again find that 25.1% of normals have a positive test. However, Labby, Shank, Kunkel and Hoagland,<sup>3</sup> in discussing cirrhosis, have concluded that flocculations from 0 to 2+ are normal. If this be true, then only 8.5% of normals in our series yielded positive Hanger tests. This may indicate that the

Hanger test is considerably more accurate (91.5%) than the thymol turbidity test, or that the latter is a more sensitive indicator of subclinical liver dysfunction. Probably the explanation for this discrepancy between the two tests lies in the difference in the chemical reactions involved and is further evidence of this difference.

Similarly, there were 845 observations on 508 hospital patients without apparent liver disease. For this same group of patients, 603 thymol turbidity tests yielded readings of 5.0 units or below, and 245 yielded readings ranging from 5.1 to 21.5. Table 7 summarizes the results in this series. Table

7 again shows that 29% of patients sick in hospital with diseases not ordinarily associated with the liver will give elevated thymol turbidity readings. Likewise, 22.6% of these patients will have a 3+ or 4+ Hanger and 46.7% will show some degree of flocculation. Here again, if we accept the criteria of Labby, Shank, Kunkel and Hoagland, the Hanger test would appear more accurate. On the other hand, it cannot be said of the thymol turbidity test carried out in the manner herein described that it lacks sensitivity. We believe that the method using the photoelectric colorimeter makes the test a highly sensitive one at pH 7.8 and that it can be thus used as a valuable, quick and easy screening test for potential liver dysfunction. The notable exceptions as pointed out above are "compensated" cirrhosis of the liver or metastatic carcinoma of the liver. These diseases may show normal thymol turbidity readings.

Likewise there were 477 observations on 124 patients with various kinds of liver and biliary tract disease. For this same series of observations there were 117 thymol turbidity determinations below 5.0 units and 360 determinations ranging from 5.1 to 38.6 units. Table 8 shows the results in this series. Inspection of Table 8 reveals that 24.5% of patients sick with liver or biliary tract disease will have negative thymol turbidity readings. Likewise, 19.1% will show a negative Hanger test, and if we consider only the 3+ and 4+ results as significant, 40.3% of patients within this group will show a negative determination.

This large and heterogeneous group of liver and biliary tract disease was therefore sorted into those with elevated icteric index and those with no elevation of icteric index; each of these categories was further divided into those with obstruction demonstrated

at autopsy or at operation and those with no obstruction. The results of this analysis are presented in Table 9.

It is apparent that in the presence of an elevated icteric index both tests are generally positive, whether the icterus is due to hepatocellular damage or to biliary tract obstruction. Perhaps the duration of the obstruction or the degree of biliary stasis and back pressure determine whether or not the tests are positive in the presence of obstruction. This is suggested by the present study, but the data available are insufficient to make this assertion. When only the cases with 3+ or 4+ Hanger tests and with jaundice are examined, it is evident that the majority again have positive tests, 61% with obstruction and 71% without obstruction (i.e., with hepatocellular disease).

The cases with no jaundice in general show normal readings in the obstructed group which consisted largely of cases of cholecystitis who entered the hospital with an attack of biliary colic and at operation were found to have an acute obstruction due to common duct stone. Presumably the obstruction had not existed long enough to cause hepatocellular damage or dysfunction and therefore caused no change in the thymol turbidity or Hanger test. The cases without obstruction and without jaundice are less clear cut. This is to be expected, since many in this group were chronic hepatitis, chronic cholecystitis without stones, mild hepatitis, or cirrhosis without jaundice. The cases of chronic or mild hepatitis showed slight elevations and the cirrhotics negative or positive readings according to the degree of hepatic compensation. The cases of cholecystitis all showed negative Hanger and negative thymol turbidity tests and might be considered to have no liver disease, the inflammation being confined to the gall bladder. There

were no stones present in the common duct in any of these cases.

Figure 3 is an attempt to summarize graphically the relationship between the thymol turbidity test and the Hanger test in cases of liver or biliary tract disease. It will be seen that in general the two tests parallel each other. When the Hanger test is definitely elevated, the thymol turbidity test will also be elevated, regardless of the specific type of liver disease. Since the Hanger test is generally recognized as a reliable indication of parenchymal liver dysfunction, it may be concluded

diseases in this group gave fairly persistently elevated readings. These were infectious mononucleosis (8 of 9 cases), virus pneumonia (3 of 3 cases), sickle cell anemia in crisis (2 of 3 cases), secondary syphilis (7 of 9 cases), malaria in crisis (2 of 2 cases), and paroxysmal nocturnal hemoglobinuria (1 of 1 case).

3. Of 477 determinations on 124 patients with liver or biliary tract disease, 360 or 75.5% showed thymol turbidity readings ranging between 5.1 and 38.6 units. The highest readings were obtained in the cases of non-obstructive

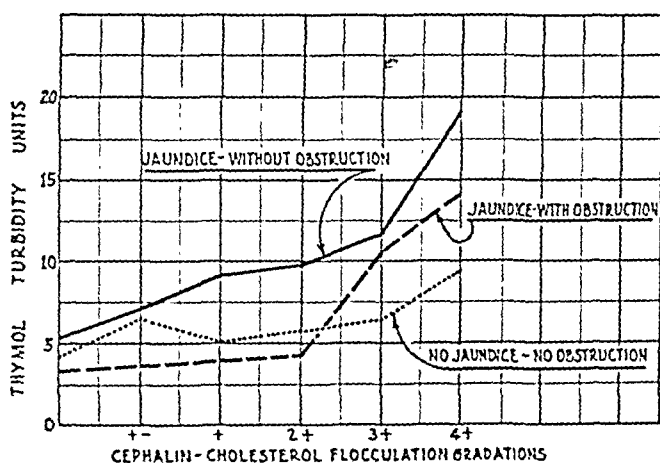


FIG. 3.—Comparison of thymol turbidity and cephalin-cholesterol flocculation test.

from Figure 3 that the thymol turbidity test is also a satisfactory measure of hepatocellular disease.

**Summary.** 1. The thymol turbidity test using a photoelectric colorimeter and standards of barium sulfate with a thymol buffer of pH 7.8 was determined on 500 apparently normal individuals. The mean value was 3.2 units with a mean deviation of 1.8 units.

2. On 527 hospital patients sick with over 100 different diseases, not usually considered to involve the liver, the mean value was 3.7 units, with a mean deviation of 2.7 units. Certain

jaundice, especially infectious hepatitis, where serial determinations gave a graphic picture of the course of the disease.

4. The thymol turbidity test readings usually parallel the readings of the cephalin cholesterol flocculation test in cases of parenchymal liver dysfunction. It is felt that this test is a sensitive, quick, and easy screening test for such disorders.

5. Refrigeration over long periods and the ingestion of a meal have little effect on sera tested with the thymol turbidity test. Inactivation by heating sera at 56° C. for 30 minutes low-

ers the thymol turbidity readings sufficiently to make them inaccurate.

Acknowledgement is made of the cooperation of the medical and nursing staffs of the hospital. The writers also

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# THE SICKLE CELL TRAIT: INCIDENCE AND INFLUENCE IN PREGNANT COLORED WOMEN

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Sickling of the red blood cells is a hereditary abnormality found in the colored race. It is transmitted as a dominant Mendelian factor.<sup>10,19,20</sup> It exists in two forms: (1) sicklemia, in which there is sickling of the cells, but no evidence of blood destruction or increased rate of regeneration, and (2) sickle cell anemia, in which there is sickling but also there is active blood destruction and such evidences of increased regeneration as reticulocytosis and nucleated red cells. Various investigators estimate the ratio of sickle cell anemia to sicklemia from 1:9 to 1:40.<sup>4,18</sup> The relationship of the two forms is not clear. Individuals with the trait are known to go through life without ever showing the anemia. The active form, if it develops, usually begins in the first two decades of life. Once the blood destructive process is activated, it does not disappear. Wintrobe<sup>22</sup> reports that he has observed remissions but never to the extent that there was no evidence of blood destruction.

A review of the literature shows no reports of studies on the occurrence of pregnancy in patients with sicklemia nor of the effects of pregnancy in sicklemic patients. There have been several reported studies of patients with true sickle cell anemia associated with pregnancy.<sup>6,9,11,23</sup> The prognosis has been observed to be poor for both mother and child. When the preg-

nancy is complicated by the active anemia, it has been suggested that patients with the active anemia are less fecund and show a higher incidence of abortions than the normal patient.<sup>13</sup>

A study was therefore undertaken to determine first, the incidence of the sickle cell trait in pregnant colored women; and second, the effects that the trait might have on the course of pregnancy. We also wished to determine whether pregnancy might activate a blood destructive process in the patient with the trait.

**Subjects and Methods.** Five-hundred consecutive colored patients in the obstetrical out-patient department and on the obstetrical ward of Roper Hospital were examined for the sickle trait. As control 250 colored females of childbearing age and 250 adult colored males were also studied. The control groups were composed of hospital employees and patients on the medical ward and in the out-patient clinics.

A drop of blood obtained from each patient was placed on a clean glass slide, a cover slip superimposed, air was expressed and the preparation sealed with melted paraffin. Microscopic examination for evidence of sickling was made immediately. The preparations were then put in an incubator at 37° C. and observed at 24 hour intervals for a total of 72 hours. Every slide was examined by each author. No slide was reported as positive unless both agreed that sickling was present.

A further control group of 105 consecutive colored patients delivered in the hospital was studied for the incidence of certain obstetrical complications. It should be noted that, in general, only patients who present some abnormality are admitted to the hospital. Uncomplicated deliveries are usually handled by the out-patient department.

**Results.** The incidence of the sickle cell trait in gravid colored women and in the control groups is shown in Table 1. One of the pregnant women was found to have mild but definite sickle cell anemia.

Twenty-two of the patients with the sickle cell trait (sickleemia) were admitted

obstetrical patients seen in other parts of the United States.

Obstetrical histories were obtained from 56 of the sicklemic patients. This group had experienced 143 term deliveries and averaged 2.55 living children each. One patient had gone through 8 normal pregnancies. Obstetrical histories were obtained from 200 gravid women who were proved not to have the sickle trait. In this group there had been 478 term deliveries with an average of 2.39 living children each.

In the 56 sicklemic patients there were 22 abortions for an average of 0.39 each, as compared with 80 abortions in the 200

TABLE 1.

Incidence of Sickle Cell Trait in Colored Persons at Roper Hospital

	Adult males	Non-gravid females	Gravid females	Total adults
No. examined .....	250	250	500	1,000
No. with Sickle Cell Trait .....	33	36	71	140
Percent with trait .....	13.2	14.4	14.2	14.0

TABLE 2.

Incidence of complications of pregnancy in sicklemic patients as compared with other gravid patients in Roper Hospital and as reported in Standard texts.

	Average as reported in standard texts	Non-sicklemic gravid cases in Roper Hosp.	Sickleemias (22 pts. studied on Obstetric Ward, Roper Hospital)
Anemia (hemoglobin).....	10 gm. <sup>2</sup>	10.4 gms.	10.41 gms. or 70%
Hemorrhage.....	5-7% <sup>11,12</sup>	2.8%	0
Premature labor.....	2.95% <sup>3</sup>	13.4%	9.1% (2)
Toxemia.....	10% <sup>14</sup>	22%	20% (5)
Stillborn.....	2.41 <sup>15</sup>	11.4%	4.5 (1)
Morbidity.....	10.5% <sup>16</sup>	18.1%	4.5% (1)
Abortion.....	20% <sup>17</sup>	64 in 394 (16.2%)	10 in 83 pregnancies (12%)

to the hospital and were followed to the termination of pregnancy and through the puerperium. At least one complete blood count, icterus index and reticulocyte count was done on each patient before labor and after delivery. X-rays of the skull were obtained on most of them as well as electro cardiograms. None of the patients showed any evidence of increased blood destruction either clinically or by laboratory determinations. The fall in red blood cell count and in hemoglobin after delivery was not abnormal.

In Table 2 we have listed the incidence of certain abnormalities found in the group of 22 sicklemic patients delivered in the hospital as compared with a control group from the same hospital and with

non sickle cell patients or an average of 0.40 each.

**Discussion.** The incidence of the sickle cell trait in the American Negro as reported by many investigators shows a fairly wide variation. Diggs, et al.<sup>4</sup> reported an incidence of 8.3% in some 2,539 examinations in Tennessee. He and his co-workers used a technique similar to that used in this study. They point out that there is a far greater tendency to report doubtful slides as negative than as positive. Hansen-Pruss<sup>7</sup> reported an incidence of 14% in 100 cases studied in North Carolina. Beck and Hertz<sup>1</sup> reported an incidence of 13% among Negroes studied in Pennsylvania.

It should be noted that special techniques were used in these studies. Tomlinson<sup>21</sup> reports an incidence of 8.2% in 3,000 Central American Negroes. His study is based partly on autopsy material and partly on wet sealed preparations.

The Negroes of the Charleston area like most of those in North America are for the most part descended from natives of West Africa. In general, these Africans came from certain fairly restricted areas lying in the coastal belt of West Africa and the Congo.<sup>8</sup> It would be purely speculative to say that the Negroes in this area of the United States represent a purer strain than those in other regions. The few studies of the trait in Africans report a much higher incidence there than in the New World. Evans<sup>5</sup> reports that the sickle cell trait was found in some 19.9% of a group of West African soldiers.

In a smaller group of Gambians, Evans found sickling in 22% of the males and in 13% of the females. Wintrobe<sup>22</sup> says that there is no difference in the incidence of the trait in the two sexes. Tomlinson<sup>21</sup> on the contrary reports an incidence of 11.35% in the female and 7.3% in the male. Our studies as shown in Table I show no appreciable difference in the incidence of the trait in males or females whether gravid or non gravid.

As far as we can determine, sickle cell does not prevent conception nor does it

interfere with normal pregnancy and labor. It is our impression that the sickle cell patient does not differ from the usual colored obstetrical patient seen in this area and as a group show no more anemia than the average of other obstetrical cases (Table 2).

One of our patients was found to have active sickle cell anemia of a mild type. It was not known whether this existed prior to her pregnancy. In none of the 22 cases of sickle cell anemia observed in the hospital was a blood destructive process initiated by pregnancy.

**Summary and Conclusions.** 1. The sickle cell trait was found in 14.2% of 500 gravid colored women in the Charleston, South Carolina, area.

2. The sickle cell trait was found in 14% of 250 non gravid colored females of childbearing age, and in 13.8% of 250 adult colored males.

3. The sickle cell trait was found in 14% of 1,000 adult colored persons.

4. Of 71 pregnant females with the sickle cell trait, 1 was found to have mild sickle cell anemia, a ratio of 1:71.

5. Sickle cell anemia does not interfere with conception nor with normal pregnancy and delivery.

6. Pregnancy did not activate a blood destructive process in 22 sickle cell patients observed through the last trimester and during labor and the puerperium.

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# PROGRESS OF MEDICAL SCIENCE

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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### HAMARTOMAS OF THE LUNG AND SO-CALLED "PULMONARY ADENOMATOSIS"

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In the past two decades, significant advances in both diagnosis and treatment of pulmonary disease have been made. Numerous clinical reports of pathologic lesions, heretofore largely demonstrated only at autopsy, have appeared in the medical literature. The increasing clinical awareness of the types of pulmonary tumors to be reviewed suggests an increasing interest in, and importance of, this subject both to the general practitioner and the specialist in medicine.

**Hamartomas.** According to Albrecht,<sup>3</sup> who first used the term, a "hamartoma" (from the Greek, meaning a failure or error) is a tumor-like malformation in which occurs actually only an abnormal mixing of the normal components of the organ. The abnormality may take the form of a change in quantity, arrangement, or degree of differentiation, or may comprise all three. The deduction to be drawn from the histologic examination of these formations is that they have originated in an abnormal mixing of the elements or from a disturbance of their development.

The 2 types of hamartoma of the lungs to be reviewed are the so-called chondroma and hemangioma.

**Chondroma.** Small, so-called chondromas of the lung are occasionally encountered as incidental findings at autopsy or as accidental findings in routine X-rays of the lungs. Their incidence varies, Altmann<sup>5</sup> reporting an incidence of 1 in every 475 autopsies, McDonald *et al.*,<sup>54</sup> 1 in 398, whereas Edling<sup>25</sup> reports 1 in every 215 cases coming to necropsy. Ordinarily, so-called chondromas vary from a few millimeters to 3 to 4 cms. in diameter, but a few tumors varying from 5 to 15 cms. in diameter have been encountered. The smaller tumors rarely, if ever, produce clinical symptoms; the occurrence of relatively large intrapulmonary cartilaginous tumors which produce clinical symptoms is distinctly uncommon.

So-called chondromas usually lie in subpleural position and rarely, according to Peters,<sup>60</sup> in hilar position. They may even lie in the pleural space and be attached by a pedicle to the pleura. These tumors, in the gross, are firm and

dense, and may be of stony hardness. They are somewhat lobulated, usually encapsulated and sharply demarcated from the lung. They are bluish-grey to white upon section and may be irregularly lobulated by traversing septa.

While the main portion of so-called chondromas may consist of cartilage, they are not pure cartilaginous tumors but contain abnormal mixtures of elements normally encountered in bronchial wall. As early as 1883, Chiari (quoted by Hickey and Simpson<sup>40</sup> and Edling<sup>25</sup>) noted the presence of fat and glandular elements in so-called chondromas and suggested the term "lipo-chondro-adenoma." Thus, in these tumors, there have been described ciliated epithelium, glandular epithelium, connective tissue, muscle, fat, and lymphoid tissue. The cartilage may be calcified, or even ossified; and, at times, osteoid and myxomatous tissue may be present. In 1904, Albrecht<sup>3</sup> defined the general concept of hamartomas (see above) and so-called chondromas have since been commonly designated as hamartomas or, more properly by Goldsworthy,<sup>32</sup> as hamartoma chondromatosum pulmonis.

In 1926 Hickey and Simpson<sup>40</sup> reviewed the subject and collected 38 cases of chondromatous tumors of the lung from the literature, to which they added 2 of their own. In 1929 Bayer<sup>6</sup> reported 5 cases, and in 1931 Klages<sup>47</sup> reported another. By 1932 Verga<sup>70</sup> had collected 61 cases, of which 3 were his own. In the same year Peters<sup>60</sup> reported an additional case, and Benninghoven and Peirce<sup>8</sup> added 2 cases, only 1 of which contained cartilage. Subsequently, Jaeger<sup>44</sup> reported 5 cases, and 1 each were added by Livingston,<sup>41</sup> Edling,<sup>25</sup> Roux-Berger and Debroise,<sup>42</sup> and Mallory.<sup>52</sup> In 1945, McDonald, Harrington and Clagett,<sup>51</sup> in a review of the material at the Mayo Clinic, discovered 23 cases of hamar-

toma, 20 of which were found at autopsy and 3 of which were removed surgically. In all of their cases various components of bronchial wall, in addition to cartilage, were found.

Most so-called pulmonary chondromas are silent because of their usually small size and intraparenchymal position. In Klages<sup>47</sup> case, the first in which the diagnosis was made roentgenologically and confirmed by histological examination of the surgically-removed specimen, the patient was free of symptoms. Similarly, in 1 of the 2 cases reported by Benninghoven and Peirce<sup>8</sup> which was removed surgically, no symptoms were present. In only 1 of the 3 cases reported by McDonald *et al.*<sup>51</sup> in which surgical removal was performed were symptoms present, and these consisted of dyspnea on exertion and a burning sensation in the anterior portion of the thorax. In Mallory's<sup>52</sup> case, where the hamartoma was removed surgically, symptoms were present. However, when hamartomas grow large they may, by external pressure, impinge upon and narrow a major bronchus to produce signs and symptoms not unlike those associated with bronchial obstruction due to carcinoma as noted by Simon and Ballon.<sup>69</sup>

From a purely theoretical point of view, there is no valid reason why a hamartoma or any other congenital malformation may not, under certain conditions, show malignant changes. It is curious, however, that this is extremely rare in cases of hamartoma chondromatosum pulmonis. Greenspan<sup>32</sup> reported a unique case of pulmonary osteochondrosarcoma which showed locally invasive features. It is probable that the origin of this tumor was from a hamartoma, although no epithelial-lined structures were noted. In the case reported by Simon and Ballon<sup>69</sup> microscopic areas indistinguishable from malignant tumor and

local invasion were also seen. No metastases from pulmonary chondromas have even been reported.

It is interesting to note that so-called pulmonary chondromas are not unique in man, but have been observed by Casper<sup>14</sup> in domesticated animals.

Endobronchial tumors composed of cartilage have been reported by Davidson,<sup>20</sup> Cracovaner,<sup>18</sup> Gebauer<sup>27</sup> and Moore,<sup>56</sup> but these all appear to be simple ecchondromas arising from cartilaginous rings of the bronchi. They are covered by the epithelium of the bronchus but contain no other elements of bronchial wall, and are not, therefore, true hamartomas in any sense. Apparently, however, true endobronchial hamartomas do occur. Ulrich<sup>75</sup> reported an endobronchial fibromyxochondrolipoma which had been removed surgically. He takes the point of view that any polypoid intrabronchial tumor containing cartilage and other tissues normally found in bronchial wall is a true hamartoma. He quotes Lindgreens as having discovered 9 other such cases in the literature. Similarly, Paul<sup>50</sup> reported a polypoid intraluminal myxochondroma which showed septa dividing a cartilaginous tumor containing ducts, cylindrical epithelium, elastic fibers and lymphoid tissue. This tumor fulfills the definition of a hamartoma.

**Hemangiomas.** Pulmonary hemangiomas, like their counterparts in the liver and in other organs, are true hamartomas, representing an alteration in quantity and arrangement of normally occurring structures of that particular organ. Whereas hemangiomas of the liver are frequently encountered, the pulmonary hemanigoma is extremely rare. Most general textbooks of pathology do not even mention the occurrence of this hamartoma of the lungs. Only Roussy and Leroux<sup>64</sup> mention hemangioma of the lung, while

Henke and Lubarsch<sup>36</sup> refer to a case described by de Lange and de Vries-Robles.<sup>21</sup> The first reported instance of this condition appears to be that of Wilkens.<sup>78</sup> An idea as to the rarity of this lesion can be obtained from the statement of Adams, Thornton and Eichelberger,<sup>2</sup> who saw only a single example in 240,000 admissions to the University of Chicago clinics. Bowers<sup>11</sup> reported a single case and found no other instance in a search of 23,897 autopsy records, while Hepburn and Dauphinee<sup>37</sup> record only a single instance in the pathologic records of the Toronto General Hospital. Sisson, Murphy and Newman<sup>71</sup> found only a single example in 19,415 autopsy records of the Johns Hopkins Hospital.

In spite of the infrequency of this hamartoma, a number of cases have not only been diagnosed correctly clinically but have also been operated upon, and these lesions have been successfully removed with amelioration of symptoms.

In 1923, de Lange and de Vries-Robles<sup>21</sup> described 2 hemangiomas in the left upper and right upper lobes, respectively, occurring in a 2½ month old infant at autopsy. This infant presented no distinctive symptoms and the lesions were unexpected findings. The tumors measured 3.0 and 1.5 cm., respectively, in diameter, and were purple in color. Histologically, they were hemangiomas of the capillary type. In 1936, Bowers<sup>11</sup> reported the case of a new-born child who became extremely dyspneic on the 2nd day and developed a hemorrhage into the pleural cavity. At autopsy, numerous raised, bluish-purple areas were found at the base of the right lung. Similar lesions were found in the left lower lobe. Histologically, the picture was that of a hemangioma.

In 1938, Rodes<sup>63</sup> observed a young man, 25 years old, who had clubbing of the fingers, cyanosis and polycy-

themia ranging between 7.1 and 7.5 million red blood cells per cu. mm. This man died suddenly from a massive pulmonary hemorrhage following an automobile ride. At autopsy, 3 purplish tumors were found in the lungs; 1 in the right middle lobe, measuring 6 cm., 1 in the right lower lobe, measuring 2 cm., and another in the left lower lobe, measuring 6 x 3 x 2 cm. All these, upon microscopic examination, proved to be large, cavernous, blood-filled spaces lined by endothelium. In this case a number of peculiar shadows had been noted in the X-rays of the lungs. These X-rays were submitted to Hirsch,<sup>42</sup> who, in 1936, had noted similar shadows in the lungs of patients suffering from polycythemia. It was his opinion that the shadows seen in Rodes'<sup>63</sup> cases were similar to the ones he had described. In the same year Edwards and Taylor<sup>26</sup> published 3 cases of what they called vascular endothelioma. Only their case No. 2 appears acceptable on the basis of the microphotographs. This case concerned a 26 year old female who developed hemoptysis. No clubbing of fingers, cyanosis or polycythemia was present. Lobectomy was successfully performed.

In 1939, Duvoir, Picot, Pollet and Gaultier<sup>24</sup> reported briefly upon a 12 year old girl who showed shadows in the X-rays of the lungs. There was no history of cyanosis, clubbing of the fingers or polycythemia, and at autopsy a hemangioma was found in the left lower lobe. In the same year, Smith and Horton<sup>72</sup> observed a 40 year old male with polycythemia, clubbing of the fingers, cyanosis and variable degrees of dyspnea and vertigo. X-ray showed a lesion in the right lower lobe, over which a bruit was heard. A radio-opaque substance was injected into the basilic vein and subsequent X-rays revealed 2 dilated ves-

sels in the right hilum communicating with the parenchyma of the right lung where the bruit was heard. These investigators regarded this lesion from a physiologic point of view as an arterio-venous fistula of the lung, which they felt was a hemangioma anatomically. This patient apparently is still alive. No operation was performed.

Plaut,<sup>61</sup> who reported 2 cases of hemangio-endothelioma of the lung in 1940, was of the opinion that these tumors represented malformations of pre-existing blood vessels. In one of his cases marked endothelial proliferation almost to the point of neoplasia was observed, and in this case there was clubbing of the fingers and cyanosis. His 2nd case, also in an adult, was a small subpleural hemangioma found incidentally at autopsy.

In 1942, the 1st case to be diagnosed correctly clinically, and in which the lesion was removed surgically, was reported by Hepburn and Dauphinee.<sup>37</sup> This patient was a 23 year old male who had clubbing of the fingers, cyanosis and polycythemia. X-ray revealed a shadow in the right lower lung field, over which a bruit was heard. A right pneumonectomy was performed, which operation was later reported by Shenstone,<sup>66</sup> and in the surgical specimen a purple, vascular, cavernous hemangioma, measuring 8 x 6 x 4 cm. was found. Several months after the operation the cyanosis, polycythemia, and the clubbing of the fingers had disappeared.

Goldman's<sup>29</sup> case concerned a male 22 years of age with clubbing of fingers, cyanosis and polycythemia. Laminograms showed a shadow in the left lung field, which, by kymographic studies, revealed in the zone of density an intrinsic pulsation which was synchronous with that of the pulmonary artery. The patient refused pneumonectomy at this time, and the clini-

cal diagnosis was cavernous hemangioma acting like an arteriovenous fistula. This patient was subsequently operated upon successfully. In a brother 32 years of age, a similar lung lesion was diagnosed by Goldman.<sup>30</sup> These 2 cases formed the basis of a subsequent report in which Goldman<sup>31</sup> pointed out the relationship of other hereditary vascular diseases to arteriovenous fistula of the lung. He is of the opinion that cavernous hemangioma of the lung is a congenital inherited anomaly and represents a variety of hereditary hemorrhagic telangiectasia.

Hemoptysis, without polycythemia or clubbing of the fingers, may be the presenting symptom, as in the case reported by Janes.<sup>45</sup> In this 30-year-old male X-ray showed shadows in both the left and right lungs. This patient had partial lobectomies performed. At the first operation a tumor "as large as a hen's egg" was removed from the right middle lobe. At the second operation, performed 9 months later, 2 hemangiomas were removed from the left lung. Microscopically, all these tumors proved to be cavernous hemangiomas. In the same year (1944) Jones and Thompson<sup>46</sup> and Adams, Thornton and Eichelberger<sup>2</sup> successfully performed pneumonectomies for clinically correctly diagnosed cavernous hemangioma of the lung. In each case X-ray evidence of a pulmonary shadow, together with clubbing of the fingers, cyanosis and polycythemia were present. In the case of Adams *et al.*<sup>2</sup> the tumors were multiple, the largest being a multiloculated, smoothly lined cavity, measuring 3 x 4 cm. This cavity communicated with the pulmonary artery through a vessel 4 to 5 mm. in diameter, with the inferior pulmonary vein through a channel 1 cm. in diameter. Microscopic examination showed this cavity (as well as the others)

to be lined by endothelial cells resting upon connective tissue. There was no hemangiomatous tissue outside these cavities. While they designated their lesion as a cavernous hemangioma of the lung, which it surely was from an anatomic point of view, a lesion similar to this, which has been referred to as "congenital arteriovenous aneurysm," was reported by Sisson, Murphy and Newman. The case of Sisson *et al.*<sup>71</sup> concerned a 45 year old negress who died shortly after an attempt was made to demonstrate the pulmonary shadow by the injection of diotrast. At autopsy a slightly bluish-colored sac was found in the left interlobar fissure. The sac was bilocular and measured 6 x 4 x 3 cm., and was found to communicate with the neighboring artery and vein. Another small but similar lesion was found in the right middle lobe.

In Makler and Zion's<sup>52</sup> case, one of the presenting symptoms was frequent nose bleeds. This 23 year old male had in addition polycythemia, cyanosis and clubbing of the fingers. X-rays showed shadows in both left and right lung fields. This patient was not operated upon and, as far as is known, is still alive. Similarly, in a recent case reported by Cleland,<sup>15</sup> epistaxis was a prominent presenting feature. In this case multiple hemangiomas were found on the face, tongue, nasal septum and buccal mucosa. The large, cavernous, pulmonary hemangioma was associated with a radio-opaque shadow, cyanosis, polycythemia, and clubbing of the fingers. This patient died 20 hours after lobectomy.

In 1947 Bisgard<sup>9</sup> performed a lobectomy for hemangioma of the lung in a 29 year old male with the usual symptoms of cyanosis, polycythemia and clubbing of the fingers. X-ray revealed a well-delineated shadow of increased density in the right lower lobe, and the



surgically-removed specimen was found to have 2 cavernous hemangiomas of the lung which showed no large communicating vessels. In this same year Sweet<sup>73</sup> performed a lobectomy for a clinically correctly diagnosed cavernous hemangioma of the lung in a 23 year old female with clubbing, cyanosis and polycythemia. Sweet, in discussing the case of Maier, Himmelstein, Riley and Bunin<sup>51</sup> mentions another successful operation for cavernous hemangioma of the lung in a child, and that he had seen a 3rd case in Dr. Alexander's clinic in Ann Arbor. Burchell and Clagett<sup>13</sup> (also in 1947) performed a lobectomy on a 20 year old male, who, since the age of 8, had developed progressive cyanosis, clubbing of the fingers and dyspnea upon exertion. This patient showed a polycythemia of 7.59 million red blood cells per cu. mm. Roentgenograms showed an irregular nodular shadow in the right lung. The right middle lobe was removed and revealed numerous greatly dilated and tortuous blood vessels. Large numbers of cavernous spaces, some looped and some ending blindly, were found. All these spaces were lined by endothelium resting upon thick walls showing some muscle and elastica. These authors speculated that these blood vessels had acquired arterial characters due to high intraluminal pressures over the years. Ten weeks after the operation the red blood cell count had fallen to 5.1 million per cu. mm., with little change in the clubbing of the fingers. In the case reported by Maier *et al.*<sup>51</sup> a superimposed bacterial endarteritis in a cavernous hemangioma of the lung was first successfully treated by penicillin before surgical removal of the lesion. In the discussion following the publication of Maier *et al.*, unpublished cases of cavernous hemangioma of the lung were mentioned by P. C. Sam-

son, L. M. Shefts, and F. R. X. Byron.

Thus, this rare hamartoma of the lung, the cavernous hemangioma, is a tumor-like, faulty developmental disease of blood vessels. These lesions may be single, but are often multiple, and may be familial. These tumors in the literature have been variously referred to as cavernous hemangiomas, arteriovenous fistulae and congenital arteriovenous aneurysms. They frequently produce shadows of increased density in X-ray films, over which a bruit is sometimes heard. When large, they act as arteriovenous shunts and often have an associated secondary polycythemia, with cyanosis and clubbing of the fingers. Variable degrees of dyspnea or vertigo may be present. Hemoptysis or epistaxis may be a presenting symptom, or rupture into a pleural cavity may occur. Frequently, other small hemangiomas or vascular naevi may be noted in these patients, as in the cases reported by Whitaker<sup>77</sup> and Lindgren,<sup>16</sup> in which pulmonary arteriovenous fistulas were associated with a family history of telangiectases. They appear to be readily diagnosable clinically, and when surgically removed the polycythemia and cyanosis disappear.

While, in general, cavernous hemangiomas of the lung, like most hamartomas, tend to be benign, it is possible that malignant tumors may arise from such developmental defects. Thus, Wollstein<sup>79</sup> described a malignant hemangioma of the lung in a 4 month old infant with multiple visceral foci. In the case reported by Hall<sup>74</sup> multiple malignant hemangiomas were found in different organs and it is possible that the lung may have presented the primary site.

**So-Called Pulmonary Adenomatosis.** In recent years a number of reports have been published concerning a

unique type of primary lung tumor occurring in man. To this tumor a variety of names has been given. Thus Löhlein<sup>50</sup> called it "cystic papillary lung tumor," Bonne<sup>10</sup> introduced the name "pulmonary adenomatosis," Taft and Nickerson<sup>74</sup> preferred "mucous epithelial hyperplasia of the lungs," Neubuerger and Geever<sup>57</sup> suggested "alveolar cell tumor of the lungs," and Simon<sup>67</sup> named it "diffuse primary alveolar carcinoma of the lungs."

These tumors are characterized by being bilateral. None of the tumors show the ordinarily accepted and classic features of primary bronchogenic carcinoma, such as invasion of bronchial wall with or without stenosis or ulceration or atelectasis. Similarly, no primary tumor is found in any other situation, so that metastatic tumor to the lungs can be definitely ruled out. In about half the cases the tumor is found localized to the lungs at the time of death, often without evidence of lymphatic invasion, and the remainder show local or distant metastases.

Grossly, the lungs may resemble the picture of a so-called "gray hepatization" of lobar pneumonia, with a sticky, gelatinous surface reminiscent of a Friedländer's bacillus pneumonia, or may present multiple elevated, poorly-defined, large and small, and at times confluent nodules of glairy, reddish-yellow, sticky tissues lying in lung parenchyma. Microscopically, an unusual type of non-ciliated, tall columnar and questionably mucus-secreting epithelium is found lining large numbers of alveoli. These cells are loosely attached to apparently unaltered alveolar walls, which show numerous papillary projections. Strands of tumor cells frequently desquamate into the alveoli. A certain amount of pneumonia invariably accompanies this tumor. The tumor cells lining the alveoli do not extend into any recognizable

bronchioles and no transitional forms between obvious bronchiolar cells and the tumor cells can be found in any situation.

This disease bears a remarkable resemblance to an epizootic disease of sheep, known variously as jaagsiekte, epizootic adenomatosis, pulmonary adenomatosis, verminous pneumonia and Montana progressive pneumonia of sheep. This disease in sheep has been thoroughly described by Mitchell,<sup>55</sup> Dungal,<sup>22</sup> Cowdry,<sup>16</sup> and Cowdry and Marsh,<sup>17</sup> and is characterized by marked inflammatory changes in the lungs, associated with an irregular proliferation of cells lining the alveoli. These cells adhere to the alveolar walls and, indeed, appear to arise from them. Such lining cells, which histologically are epithelial in appearance, vary from cuboidal to columnar, are not ciliated, show papillary infolding into the alveoli, and apparently are not continuous with bronchiolar epithelium. When fully developed, the microscopic picture resembles an adenoma or adenocarcinoma, but the cells are regular and metastases do not occur.\*

From sheep affected with jaagsiekte, Dungal<sup>23</sup> isolated a virus with which he can reproduce these lesions in the lungs of sheep. The virus does not appear to be pathogenic for man, as shepherds who are housed with these sick animals for relatively long periods do not contract the disease. Hildebrand<sup>41</sup> has recently reported an instance of pulmonary adenomatosis in which the patient was a ranch wife who lived on a large sheep ranch in Montana where jaagsiekte was endemic. He speculated upon a possible common origin of the human and sheep diseases. Attempts to transmit the disease to various laboratory animals with human autopsy material by Richardson,<sup>62</sup> Sims,<sup>70</sup> and Wood and Pier-

\* One exception is furnished by Aynard, Peyron and Falchetti, cited by Dungal.<sup>27</sup>

son<sup>56</sup> have been uniformly unsuccessful. The etiology of this disease in man is unknown.

In their excellent review of this subject in 1942, to which the reader is referred for bibliography up to this date, Neubuerger and Geever<sup>57</sup> collected from the literature 43 cases of unusual tumors of the lung. All of these collected cases showed characteristic cuboidal to columnar epithelial cells, with and without papillary infolding, lining large numbers of alveoli in both lungs. In all cases the usual bronchogenic origin was excluded. No evidence that the lung lesions were metastatic was present. Of these cases, 24 (or 56%) showed metastases. These metastases, generally speaking, were either local or isolated in far-removed organs. In the balance of cases the lesions were confined to the lungs at the time of death. To these tumors Neubuerger and Geever<sup>57</sup> gave the name of "alveolar cell tumors of the lungs." With the exception of metastases, their collected cases otherwise appeared to be strikingly similar if not identical with so-called acceptable cases of "pulmonary adenomatosis" of Helly,<sup>35</sup> Löhlein,<sup>50</sup> Oberndorfer,<sup>59</sup> Bonne,<sup>10</sup> Richardson,<sup>62</sup> and Briese.<sup>12</sup> In 1913, Sims<sup>70</sup> and Bell<sup>7</sup> each reported a case of so-called "pulmonary adenomatosis" in which the lesions were confined to the lungs and showed no local or distant metastases. The following year Taft and Nickerson<sup>74</sup> added 2 instances of this disease, to which they gave the name of "mucus epithelial hyperplasia of the lungs." Here, again, the lesions were bilateral and no metastases were present. In 1944 Accavado, Giuntini and Croxatto<sup>1</sup> reported a case which clinically simulated military tuberculosis. In their case tumor cells were found in the sputum, and autopsy showed the lesion to be bilateral, without either local or distant

metastases. In 1945 Wood and Pier-son<sup>50</sup> added another in which the diagnosis was made on surgical material removed at operation. Lobectomy was performed, but circumstances subsequently proved that the lesion was diffuse and bilateral. No metastases were present either locally or in distant organs. Ikeda<sup>43</sup> reported 2 cases, only 1 of which appears to be acceptable, as his 2nd case showed a gross bronchial tumor. In this same year (1945) Geever, Carter, Neubuerger, and Schmidt<sup>28</sup> reported 6 additional cases of "alveolar cell tumor." In 4 of these metastases were present. In all, the usual bronchogenic type of tumor was excluded.

In 1947, Simon<sup>67,68</sup> reported 2 cases. In 1 the tumor was bilateral and was confined to the lungs at the time of death, and no mediastinal lymph node metastases were present. In his 2nd case the lesions were found to be bilateral, with metastases to the brain. No mediastinal lymph node metastases were present. In this case it was demonstrated for the first time that the diagnosis could be established before death by lung puncture. In this same year Alexander and Chu<sup>4</sup> reported an additional case.

The histogenesis of so-called "alveolar cell tumors of the lung" raises the interesting and controversial question regarding the presence and nature of alveolar lining cells. The evidence for and against the existence of lining cells, and whether they are epithelial, endothelial, or both, is too involved to be included in a review of the present scope. It appears to be the opinion of most authors publishing on this subject that the bulk of experimental and clinical observations strongly suggests that alveolar epithelium does exist and that, under proper circumstances, it may proliferate and may, indeed, give rise to tumors. In all the reported

cases of the type of tumor under discussion the various authors have stressed the inability to demonstrate, either in multiple random sections or serial sections, that these tumors arise from bronchiolar lining cells.

Herbut<sup>38</sup> has suggested that these tumors arise from bronchiolar epithelium, particularly in foci of bronchiectasis. However, bronchiectasis in so-called "alveolar cell tumors of the lungs" appears to be an extremely infrequent and inconstant accompanying condition. Since the lesion is bilateral and frequently shows no evidence of lymphatic invasion, it appears unlikely that the tumor cells arise from bronchiolar epithelium. The possibility that this may be a tumor of multicentric origin cannot be excluded. While it is true that occasionally metastatic tumors may line alveoli, it is unlikely that this variety of tumor is metastatic from some cryptic focus, as Herbut<sup>39</sup> further suggests.

The variety of names applied to this tumor appears to have arisen largely from the controversy concerning the existence of epithelial alveolar lining cells. Neuburger and Geever<sup>57</sup> chose the name "alveolar cell tumor" without intending to connote the histologic origin of the cell. Simon<sup>67</sup> contends that if the word "cell" is omitted and the condition described as "diffuse primary alveolar carcinoma of the lungs" de-

finite reference as to possible cell origin is omitted. The terms "pulmonary adenomatosis" and "mucus epithelial hyperplasia of the lungs" may be misleading, for, in spite of the benign appearance of some of these tumors histologically, and particularly when they are as yet confined to the lungs, this tumor appears to behave as a slow-growing but eventually metastasizing carcinoma. The case reported by Dacie and Hoyle<sup>19</sup> showed transition from intra-alveolar hyperplasia, which on histological grounds was taken to be benign, to an infiltrating carcinoma. It is possible that the degree of pneumonia which invariably accompanies these tumors may be the cause of death before metastases have had time to develop.

The clinical course and clinical findings in diffuse primary alveolar carcinoma of the lungs are not sufficiently clear-cut to permit an unequivocal clinical diagnosis. Cough, X-ray evidence of bilateral lung consolidation which varies in size from time to time, absence of eosinophilia (Loeffler's syndrome should be excluded), with or without hemoptysis, and the progressive nature of the disease are suggestive features. The diagnosis, however, may be established during the life of the patient by histologic examination of aspirated lung tissue.

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# PREVENTIVE MEDICINE AND EPIDEMIOLOGY

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## TROPICAL ENVIRONMENT AND COMMUNICABLE DISEASE

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A direct result of this shrinking world<sup>76</sup> is not only a smaller world in terms of travel time but a better understood world<sup>13</sup> through greater familiarity with other places and other people. The concept of tropical medicine consequently has changed from that of a peculiar group of diseases persisting in peculiar parts of the world to an appreciation that tropical medicine is general medicine,<sup>19</sup> that few truly tropical diseases exist. For various reasons, including a favorable climate or a climate not unfavorable,<sup>54</sup> a goodly number of infectious processes have their greatest incidence in the tropics, but most of them also extend widely into subtropical regions and not infrequently into temperate areas. The infectious agent of amebiasis, a favored example of a tropical disease, was first determined in the feces of a patient in Archangel,<sup>52</sup> close to the Arctic circle; its greatest recorded epidemic in modern times<sup>61</sup> came from a slip in sanitation in a midwest American city.

Typhus is anything but a tropical disease.<sup>31</sup> The peculiarities of clinical disease and of disease distributions in the tropics are largely a function of the tropical environment, a tropical environment that is complex, by no means uniform and not determined by the simple quality of latitude or other geographical character.

The conventional view of the tropics as a steaming jungle is correct only in part, although it holds for the Guianas, vast areas of the Amazon and Congo basins, and the low African west coast.<sup>3</sup> What is necessary to remember is that conspicuous differences in climate and environment exist within the same latitude.<sup>30</sup> The trade winds make life possible in numerous tropical islands, the monsoons lead to climatic attributes of another order, and altitude produces an entirely agreeable climate on the high plateaux of the tropical Andes, the highlands of East Africa and Rhodesia, and in the Indian hills.

Tropical climates<sup>73</sup> are sometimes

hot and moist; the rain-forest climate sometimes hot and dry, as of the grasslands and the desert, or alternately wet and dry, by reason of the monsoons. All have in common a lack of change, which is as true of the unbroken, unvarying coolness of the hill district of India as of the heat of Bombay or of the Amazon valley. The main difficulty<sup>6</sup> about tropical climates is not so much the high level of maximum temperatures as the consistency with which high levels are maintained. That the monotony of the tropical climate has implications beyond disease and human comfort<sup>7</sup> is the belief of Ellsworth Huntington<sup>39</sup> and others who correlate the development of civilization and the energy of nations<sup>37</sup> with climates of marked seasonal variation.

Geography determines, then, the boundaries of the tropics and the subtropics that extend beyond. It determines some of the general characteristics of those regions, and through its influence on the weather importantly governs climate. But environment is more than climate, it is more than the whole of the natural surroundings of a region; it represents all of the external conditions which have an effect on the life and development of an organism. The universe of living things, man and all others, enters just as directly into what constitutes environment<sup>40</sup> as do the more evident inanimate physical factors by which one part of the world is so commonly distinguished from another. Many times it has the greater force in determining the nature of man's existence, this being particularly true of disease—what it is and where it tends to be.

*An Ecologic Concept of Communicable Disease.* Increasingly, communicable disease comes to be understood as conforming to the laws of ecology,<sup>41</sup> with its distributions in time and space and its clinical nature the

manifestations of a variable biologic equilibrium which involves two contending species, a host and an agent of disease. Thus the consideration of environment as a determining influence on diseases of man<sup>42</sup> is more than the action of climate on a human host, which is the emphasis so commonly taken. The environmental influences exerted on the infectious agent can be equally significant. Additionally, the several elements of environment often act independently of the particular host and agent directly concerned with a disease, to determine in important degree the distributions and even the clinical nature of the process; this through such epidemiologic factors as the reservoir of infection and the mechanism of agent transmission from host to host.

In simplest terms, ecology deals with the relationship between various living organisms in an environment and the reaction they evidence to their animate and inanimate surroundings. It has to do not only with individuals and with communities of those individuals, but with species and their interrelationships. Those relations are recognized<sup>43</sup> as particular, continuous, reciprocal or indissoluble. Translated into terms of communicable disease, the kinds of infection are variously natural, foreign, refractory, accidental or casual.<sup>44</sup>

Health and disease, like the fundamental matters of existence and survival, are thus the results of an ecologic interplay.<sup>45</sup> Because communicable disease is so evidently a matter of the reciprocal influence of 2 organisms, of a host and an infectious agent, the ecologic interpretation of disease phenomena is best accomplished by separating the disease agent from other elements of the environment; and looking upon disease processes as the interaction of a triad, a host—and man is the

primary concern—an agent of disease, and lastly the remaining features of environment.

Beyond the matter of survival, the health of an individual or of a species represents a dominance of positive adaptations to its particular environment, either through greater numbers of positive than negative adaptations or because they are more heavily weighted. Otherwise, the organism can scarcely endure. Disease from the standpoint of man is a negative resultant of the forces of ecology, the extent and seriousness of which is dependent upon the kind of balance, the nature of the biologic equilibrium, currently existing between human host and agent of disease. This is in every sense a varying equilibrium and the costs of the negative adaptation are assessed in terms of the clinical nature of the disease that results, the number of persons affected, and the places and duration of the process. Epidemiology is medical ecology.

With the biologic adjustment between host and parasite fairly evenly weighted, with the disturbances in equilibrium of limited degree, a disease like bacillary dysentery<sup>91</sup> results—from a world standpoint<sup>94</sup> widespread and readily transmissible, its epidemics relatively infrequent and usually inconsequential, not too exacting in terms of death and disability except for infants and the aged, and not too susceptible to measures of control. By contrast, cholera illustrates a less satisfactory adaptation between host and parasite. The circumstances of environment must favor its spread, the swings in disease prevalence are greater, and the cost in cases and deaths can be appreciable. This serves likewise to limit its prevalence to comparatively few parts of the world. Cholera has many times shown its ability to strike widely when favoring

circumstances exist, but in the absence of their continuing presence it fails to establish itself. Cholera in Vermont in 1832 and the epidemic of Lake Champlain<sup>10</sup> are little more than memories.

The ideal compromise in the host-parasite relation would mark the ability of both elements to survive in the presence of a nicely balanced equilibrium where neither is killed off and neither suffers greatly. But the search of life for the perfect equilibrium is never rewarded. As the result of long association it may happen in a degree, where infection occurs without recognizable clinical symptoms, definable only by serologic or other means and called latent infection, a circumstance rather common with diphtheria. Since all ecologic relationships are temporary and tend from time to time to be disturbed, sometimes through one factor and sometimes through another, it follows that epidemics of frank clinical diphtheria are not unexpected.

An infinite number of minute differences in the life history of people, of parasites and of insect vectors of disease, govern the implantation of disease endemically and its epidemic spread. From this it follows that similar diseases and similar epidemics may arise from dissimilar causes. This requires that all factors entering into disease production and disease distributions be kept in view at the same time, and each in relation to the other.<sup>67</sup>

In accordance with the principle found suited to the non-living world, modern biologic investigation endeavours to ask nature questions one at a time and, from a series of partial pictures, reconstruct the existing whole. Lee<sup>50</sup> warns against pursuing this too far; that a living organism is not a collection of a few simple mechanisms integrated by simple mathematical relationships; it is not merely the sum of



its component parts. Variables are linked together in multiples and by anything but simple linear relationships. It frequently becomes necessary to study living nature in many dimensions simultaneously and to analyze the resulting complex data statistically rather than attempt the simplification<sup>52</sup> which is the modern tendency.

Present day epidemiology stresses the importance of the agents of disease, largely by reason of the better methods and the greater ease with which they are measured and appraised. The ecologic approach requires that the agent be integrated into the larger fabric of the environment. The causes of an epidemic are not solved when the infectious agent becomes known, even though the ordinary methods of spread are understood. A person in the communicable phases of an infectious disease, introduced into a circle of susceptible hosts, or even a number of such persons, is not alone sufficient for an epidemic, as the recent experience of United States soldiers returning from tropical regions<sup>53</sup> well demonstrates. Susceptible human hosts for almost any of the known communicable diseases are resident throughout the world. Under modern conditions of commerce and travel few countries escape occasional importation of infection. In certain regions one such circumstance suffices for a frank epidemic; at other times and in other places the disease does not strike, in spite of numerous community and individual exposures. The answers may well be sought in the environment.

*An Interpretation of Environment.* The limited perspective with which environment is commonly viewed is open to improvement by considering it as composed of three major elements—the physical environment, the biologic and the socio-economic.

**Physical Environment.** The physical surroundings of man are so evident and immediate an influence on communicable disease that for many years that was the whole interpretation. The concept of a broader content came only gradually. The same close association with the everyday affairs of life was also a likely reason that in early historical times and through the Middle Ages<sup>54</sup> the causes of communicable disease were sought in cosmic and meteorologic influences. Every description of a disease opened with word about season, temperature, locality or other similar feature. When etiologic discoveries explained in a more rational way the behavior of malaria, plague, and so many others, the action empirically attributed to an environment was readily turned to an understanding of how those forces affected host and parasite, contributed to insanitary conditions, and thereby affected the nature and distribution of disease.

From the beginnings of tropical medicine, climate<sup>54</sup> and the weather<sup>54</sup> have always had full emphasis; to an extent that other important environmental features were sometimes overshadowed. The definition of climate as the normal or characteristic weather conditions over a long period and in a particular locality or region, is none too definite. Smith<sup>55</sup> adds something in stating it to include all solar and terrestrial features and influences which affect animal and vegetable life; but it remains to list the better established components,<sup>55</sup> which are atmospheric temperature, relative and absolute humidity, rainfall, movement of air and prevailing winds, sunshine, barometric pressure, and atmospheric electricity. Under all circumstances climate is a moving, shifting epidemiologic influence.

Improved methods of measurement were suggested earlier as basic to a

better understanding of the influences of environment. The climatic features of the physical environment promise more than most elements of the biologic or socio-economic environment, for physical determinations of temperature, humidity, wind velocity and rainfall have reached a high level of accuracy and ease of application. In many localities records are available over long periods. The difficulty is not with the individual elements, but with the combined effect that results, for example in the matter of temperature.<sup>66</sup> That air temperature and humidity are inseparably linked is universally known, but the added effect of wind and solar radiation is not so generally appreciated.<sup>27,46,74</sup> The physiologic action on the human host is from a combined effect. The possible combinations are great, and no better example is to be had of the desired ecologic interpretation, an assessment of values through correlation of all factors. The kathermometer<sup>35,53</sup> has contributed improved technical method. A calculated value, the effective temperature,<sup>78</sup> gives expression to the combined effect of temperature and wind, for an improved,<sup>50</sup> but not a final answer.

The physical environment does not end with climate and weather. A difference in geologic structure was found by Buxton<sup>9a</sup> to explain the freedom from filariasis of the east side of the island of Esperitu Santo, in contrast to heavy infection on the west. The east side was a porous coral chalk, the west side thick old volcanic soil with standing water that gave a fine breeding ground for the mosquito vector. Soil is no longer looked upon as an epidemiologic influence by reason of its miasms, but Augustine and Smillie<sup>4</sup> have shown its character, sandy and moist, and its temperature, to influence the frequency and length of life of hookworms.

**Biologic Environment.** The biologic component of environment can be taken to include the universe of living things that surrounds man, all else than man himself. The ecologic and epidemiologic influences of the biologic environment in respect to mass disease of man are within two principal areas; the activities of animals and plants as sources and reservoirs of infectious agents, and secondly the considerable influence they exert as vectors of disease. The function of the biologic environment is not limited to these indirect activities, despite the profound influence they have on disease prevalence in man. Repeated evidence is to be had of a direct action on one or other member of the particular host-parasite complex. Resistance of the human host is favorably or adversely altered, the action of the agent inhibited or enhanced.

Three principles govern the efficiency both of arthropods as vectors of human disease and of other animal species as reservoirs of infectious agents. These are the character of the host-parasite relation between species and agent concerned, population numbers of vector or animal reservoir, and the host relations of the species to man. The first is inherently, but not wholly, a biologic matter, a private and particular concern of the individual animal species and the parasite. The other two bring into play the whole ecologic complex.

Populations of arthropod vectors and animal reservoirs are intimately related to the physical environment, for as the physical environment acts on man as a host, so likewise it affects these other hosts; to the extent that entomologists approach the problem of insect outbreaks<sup>84</sup> as epidemiologists study disease, ecologically. Numbers are also governed by the socio-economic environment, to the extent that man

participates in direct destruction of vector or reservoir, or his manners and habits of life affect their well-being.

The socio-economic environment has a dominating effect on the host relations of vector or animal reservoir to man, the third consideration. Effective production of disease depends upon the extent to which the occupation, habits and customs of man bring the two into contact, the ease of transfer brought about by density of population and deficiencies of housing, and similar influences aside from the basic biologic suitability of the association.

**Socio-economic Environment.** The socio-economic component of environment is that which relates to the association of man with his fellow man. In simplest terms it is human ecology. L. J. Henderson<sup>70</sup> has remarked how the strongest feelings exist about the sociologic properties of the environment, but with little intellectual awareness of which ones are most important. Quantitative information is grossly inadequate; and perhaps of greater concern, a common lack of satisfactory methods for study and appraisal of these features as an influence on mass disease of man.

Examples of broad and long continued action are readily had; that of the African slave trade<sup>71</sup> in the spread of tropical disease to the Americas, not to mention war,<sup>72</sup> which is the most upsetting factor that can disturb human ecologic relations. The human factor is as evident in the small affairs of everyday life, the urge to herd together in concentrated groups, to wander widely over the earth, the close association with a variety of domestic animals, and the diverse food habits of man.

Since economic life so largely determines social existence, the two are taken as a single factor. The socio-economic environment exerts an in-

fluence on disease of such moment as to permit generalization, that the lower the social economic status, the higher the prevalence of disease. This holds for communicable and for non-communicable processes, for such diverse conditions as cancer<sup>73</sup> and rheumatic fever.<sup>74</sup> Its importance is reflected in a current appraisal by Kauntze<sup>75</sup> of medical problems of the tropics as being chiefly due to a general lack of education, a poor social economy, and a lassitude partly attributable to the sapping of human energy by endemic disease.

A solid attack on the factor of nutrition is underway—broadly and in relation to principle in temperate zones, to far less extent in relation to the specific problems of the tropics. The need is appreciated<sup>76</sup> for precise data on the effect of work on caloric and other nutritional requirements, on water and salt requirements in the tropics,<sup>76,77</sup> and on the effects of various stresses and mild disease processes on nutritional requirements and fitness<sup>77</sup> of man. The peculiar requirements of the white visitor or temporary resident continue to be the commoner interest, in more recent years largely because of war interests,<sup>78,79,80</sup> but the fundamental problem is that of the native.<sup>79</sup>

Housing and the allied problem of crowding are potent influences; likewise the habits and customs of people, both those inherent or of natural evolution, and those arising artificially from religious or other tabu. All enter directly into environmental sanitation, and direct attention to the principle too often forgotten these days, that the first need of a people starting toward a public health is to get up out of their own dirt. A letter of recent months from a young colleague just arrived in the tropics expressed the opinion that the single most important local objective as he saw it, was to get people to put their feces in one place.

Little quantitative information exists about the influence of education, clothing, income and social welfare on diseases of the tropics. The recently appreciated significance of psychologic and mental reactions as an influence on susceptibility to disease has scarcely been extended to tropical medicine, other than to the white populations<sup>44</sup> and military forces.<sup>82</sup> Much of the effect heretofore attributed to the physical and biological environment, undoubtedly rests within this field of socio-economic environment, a most underdeveloped interest of epidemiology, tropical or otherwise.

**A Basis for the Study of Environment.** The ecologic approach to the study of communicable disease has been based on an appraisal of host-parasite equilibrium, a phenomenon in turn dependent upon the innate characteristics of the 2 primary factors under the influence of environment. This is an old concept for the biologist in relation to the individual.<sup>55</sup> It is an equally valid approach to the problems of the community—to mass or herd disease—where more or less disease depends upon a more or less temporary collection of the same or different species. Environment has been separated into three components.

From these premises a pattern emerges for the study of the general environment as an influence on disease—a differentiation of 6 statistical cells into which may be set those phenomena attributable to the three features of environment, physical, biological and socio-economic, as each acts on host or on agent.

**Criteria for Appraisal of Effect.** Two criteria are useful in weighing the effect of environment on a disease. The clinical nature of the process is one, the peculiarities of frequency distribution within time and space is the

other. Either or both may be in evidence.

Diphtheria as a faucial infection is uncommon in the tropics,<sup>40</sup> although its considerable frequency as an infection of the skin<sup>86</sup> suggests that more attention be given this possibility in sub-tropical areas. Despite the comparative infrequency of the clinical disease, evidence from a variety of tropical areas indicates a widespread distribution of the infectious agent,<sup>21</sup> equivalent to that of temperate regions. Clinical differences in amebiasis under tropical and temperate conditions are noteworthy.<sup>15</sup> Scarlet fever,<sup>20</sup> poliomyelitis,<sup>38</sup> and others of the common infections of childhood show similar clinical modifications, although the agent is as extensively prevalent in the one region as the other.

Individual and peculiar distributions of communicable disease by reason of environmental effect are well known, numerous and precise: Oroya fever<sup>34</sup> in certain valleys of Peru and at prescribed altitudes, a factor of the biologic environment; yellow fever dominantly influenced by the physical factor of environment;<sup>70</sup> cholera so strongly socio-economic,<sup>11</sup> and yaws<sup>83</sup> similarly.

**Types of Environmental Action.** Each of the three factors of environment as it acts on host or on agent of disease is now presented, with no thought that a particular complex represents a pure line of action. That is characteristic neither of ecologic nor epidemiologic relationships, for the observed effect is usually of multiple origin. The patterns offered indicate a dominant, rather than an inclusive action.

**Physical Environment-Host.** No single feature of the tropical environment has been accorded more attention than physical factors as they operate on the human host. This is largely

confined to the artificial tropical host—the more or less temporary white resident<sup>59b</sup>—with little attention to the true native host. Although the tropical climate exerts no selective action,<sup>26</sup> the effect on the uninitiated is greater. Many escape tropical disease, but no one escapes the climate.<sup>5</sup> When first exposed to hot environments most individuals are incapable of working strenuously or for prolonged periods. By a process of acclimatization man adapts himself to work in the heat,<sup>6</sup> through a complex physiologic readjustment<sup>21</sup> which cannot be defined adequately or determined completely by simple physiologic measurements. The problem varies between hot dry<sup>1</sup> and hot moist<sup>55</sup> climates, a matter of no small consideration in recent military activities.<sup>16a</sup> The literature on the manifold physiological disturbances associated with adjustment to the whole tropical climate and to single climatological factors<sup>17</sup> is widely scattered and not readily accessible, but a good start can be had with the reviews of Sundstroem,<sup>80</sup> Ward<sup>59</sup> and Talbot.<sup>51</sup> That such influences of climate on the human host are a function of susceptibility to communicable disease is readily evidenced by every principal group of tropical infections, perhaps best by the enteric diseases. Kligler<sup>48</sup> brings out that different individuals and indeed the same individual, are more or less susceptible at different times.

Despite the penetration into matters concerned with acclimatization of the unaccustomed, and the effects of the various physical components of the tropical environment on the human organism,<sup>59a</sup> a basic approach to the host factor is in much the same situation as in temperate regions, where the physiologic and anatomic characteristics which condition response to an invading parasite are a most neglected

and yet important aspect of the problem of infection. To take a specific example, the need is cited for a workable knowledge of the pathogenesis of plague.

**Physical Environment-Parasite.** In speaking for a broader perspective for bacteriology Hudson<sup>37</sup> states that the importance of environment is a principle of tropical medicine. The full potentiality of microbiological technics in the study of tropical disease is believed to reside in the better understanding of the manner in which environment affects infectious agents, and how their behavior in nature is influenced by that factor. One common manifestation is in the determination of disease distributions.

The yellow fever virus has well prescribed temperature limits within which it develops in the mosquito, most rapidly and efficiently at 38° C. requiring a 9 day interval at 30° C, 12 days at temperatures of 25° to 28° C, while below 23° C infection does not follow.<sup>18</sup> The result is a climatic limitation of distribution to the warmest climates and the hottest seasons. Well recognized isotherms have been established for malaria. The distribution of filariasis is governed by the failure of the agent to pass the necessary developmental stage in the mosquito at temperatures ordinarily encountered north of 40° latitude.<sup>58</sup> The vector exists much beyond that limit. The agent is thus the susceptible part of the cycle, through an influence of the physical rather than the biologic environment.

**Biologic Environment-Agent.** The number and complexity of the living things that surround man alone suggest that many direct influences are exerted by the biologic environment on the agents of human disease. The additional indirect action through the mech-

anism of transmission by arthropod vectors also governs their effectiveness.

Direct influences of the biologic environment are on numbers of the agent and on its biologic characteristics. Populations of infectious agents in a locality are limited through mechanical or other destruction by living plants and animals, by entry into non-susceptible hosts or through ingestion as food or with food. Numbers are increased, and sometimes the very existence of an agent is determined by the presence of sufficiently numerous immediate or intermediate hosts.

The biologic characteristics and pathogenicity of many agents of human disease are modified by residence in hosts of other species, sometimes to the advantage and sometimes to the disadvantage of man. This takes place in nature and has been repeatedly accomplished experimentally. The variation among strains of influenza virus<sup>56</sup> as they pass from person to person in the course of an epidemic is characteristic of that disease. That deviation from the modal form of the particular species is brought about in passage through animal hosts is suggested by studies such as those of Zelle<sup>95</sup> on *Salmonella typhimurium* in mice. Evidence was provided of discontinuous variations of smooth and rough forms, and their selection by the environment in the infected host. Further suggestion of broad and long continued action is had from the established host specific variations that exist among the brucella, the pox diseases, the hemolytic streptococci, the psittacosis-lymphogranuloma viruses and others. Experimental alteration of biologic characteristics through continued contact with animal tissues has been accomplished with all principal classes of disease agents, to such important purpose as the modification of yellow fever virus by mouse and chick embryo tissues, which gained

a favorably modified strain that made wide scale immunization feasible.

The efficiency of a vector in transmitting an agent, and the resulting effect on the distributions of a disease, is determined by its biologic characteristics and by its numbers. Man and guinea pig are equally susceptible to *R. prowazeki* but the guinea pig never contracts typhus in nature, because *Pediculus humanus* is not a natural parasite. *Trypanosoma cruzi* remains viable when artificially introduced into the bedbug *Cimex lectularius*, the macerated tissues produced the disease in experimental animals, and yet this arthropod does not become infected in nature. The triatoma and other reduviid species are so infected, but as a consequence of their distribution the disease is one of warm countries. The ecologic relations appear more complicated than a simple matter of limited distribution of susceptible intermediate hosts and adequate vectors, for both vectors<sup>93</sup> and mammalian hosts<sup>49</sup> have been recognized in California and more recently in Texas,<sup>62a,62b</sup> with no instance of natural human infection yet reported. The reason may rest in matters of the socio-economic environment, or less opportunity for infection because the agent is less frequent in nature, but at any rate there is an epidemiologic problem that warrants further exploration ecologically.

The size of the vector population has much to do with the frequency of the human disease in a given locality. Actual numbers are conditioned by speed of development, length of life, fertility, food supply<sup>92</sup> and a variety of other factors that bring into play the other two great divisions of the environment, physical and socio-economic. Buxton<sup>96</sup> summarizes his experience in stating that many of the periodical changes which may be ob-

served in the abundance of insects are due to climatic changes. The factors which limit their geographic spread are also frequently climatic.

Rainfall is so closely associated with the incidence of malaria that rainy years have come to be appreciated as malaria years through the favorable conditions provided for mosquito breeding and the resultant numbers. The rule is regular, but not invariable. One of the most striking examples of the effect of environment on disease was epidemic malaria in Ceylon<sup>59</sup> in 1935, due to drought rather than excessive rainfall. The outbreak occurred in the most healthy and prosperous part of the island, where rainfall was usually high and malaria infrequent. A prolonged drought was followed by a few rains which collected in shallow pools along river banks and streams, providing excellent breeding places for the prevailing *Anopheles culicifacies*. But the resulting epidemic, which led to some 80,000 deaths from malaria in the space of 7 months was not wholly the result of physical environment acting through biologic environment on a disease agent. The socio-economic environment also came into play, for the drought led to a failure of crops, an altered nutrition, and consequent decreased resistance of the human host. All three great classes of the environment took part in the genesis of the epidemic through action on both host and agent of disease.

Although gross numbers of the vector affect disease distributions, the more critical consideration is the number of infected vectors that make contact with the human host. The aggregate of effective vectors is determined by influences of the environment that are variously biologic, through the habits and behavior of the arthropod vector; physical, through wind direction from

infected native villages and swamps; and socio-economic, in relation to habits of clothing and customs of housing. More direct and precise examples of environmental determination of vector efficiency are the effect of humidity on activity and behavior<sup>60</sup> of terrestrial insects; the increasing activity of many insects with a falling barometer; and the lessened activity of *Phlebotomus* in windy weather.

That ecologic ease and not simple opportunity governs transmission is well brought out by circumstances in the Pacific area during the recent war. Dengue and filariasis were common diseases. Dengue spread broadly and rapidly from New Guinea to Hawaii,<sup>60</sup> tracing the course of the war island by island. Filariasis was encountered in appreciable numbers,<sup>60</sup> since some 14,000 patients with that diagnosis were evacuated to continental United States. But filariasis did not spread like dengue, although the same social environmental conditions of travel and traffic, customs and habit prevailed; and the vectors of both diseases were widely distributed throughout the Pacific.

**Biologic Environment-Host.** The influences of the biologic environment on the human host are sometimes broad, vital and fundamental; as when they relate to competition for food and the predatory action of species, one on the other and on man. They are sometimes contributory to host susceptibility, as through activity of strictly pest insects on the physical state through loss of sleep, allergic sensitivity or psychologic disturbance. There is the powerful influence of chronic low grade infection and of the parasitisms which lead to the tropical anemias. The effect may be as precise and direct as the streptococcal and staphylococcal infections made possible by tissue injury through the bite of sandflies.

The main epidemiologic interest is with the reservoirs<sup>36</sup> of human infection that rest in plants and animals. Some of the relations are simple and direct, as the food poisoning that results from *Salmonella* and an infected animal host. Others are complicated and highly selective in their determination of disease distribution, as the illustration to follow shows.

Although *Clonorchis sinensis*, the liver fluke of man, cat, dog and other fish eating mammals has been carried to all parts of the world by emigrants from the endemic areas of the Orient, no new focus of clonorchiasis has ever developed. The infection chain is man or reservoir host—snail—fish—man. Snails ingest infected feces of mammalian hosts, cerceriae from snails encyst in the musculature of fish and pass to man when fish are eaten raw. The adult parasite has little if any host specificity, for most mammals appear susceptible. The cerceriae likewise show no specificity, since over 40 species of fresh water fish of at least 4 different families have been reported naturally infected with metacerceriae. The miracidium is highly specific and limited to a few species of snails having strict Asiatic distribution. The failure of the infection to penetrate widely is due to the absence of appropriate snail hosts and the inability of the miracidium to use local snail species. A socio-economic environmental consideration likewise enters. Clonorchiasis is very common in dogs and cats of central and north China, as far as Peiping, but extremely rare or absent in human populations since fish are habitually cooked before eating. Such interrelated host manifestations are basic to an understanding of mass disease of man.

**Socio-Economic Environment-Agent.** Many diseases called tropical are merely diseases which have their great-

est distribution where social and sanitary conditions are primitive or grossly defective, and nowhere is this more the case than in the tropics.<sup>12</sup> Even a disease like plague has its socio-economic component although so clearly a matter of biologic environment, of rats and fleas and other intermediate mammalian hosts and insect vectors. The commerce in grain, the houses in which men live and the customs they practice favor the activity of these biologic elements of the environment.

In illustration of the influence of the socio-economic environment on an agent of human disease, attention is directed to the great frequency of trichinosis in temperate regions and its essential absence in the tropics. Explanation of this behavior has been sought in differences in light, temperature, and humidity. The action of the social environment, however, offers a reasonable explanation. The customs and practices of tropical man lead to everything of the porcine host being eaten, with no remainders for the pig; consequently, an interruption of the chain of infection. The contrasting frequency of human infections with *Taenia solium* is by reason of the pigs ranging close to the house, human feces being similarly deposited and a resulting high rate of transmission.

**Socio-Economic Environment-Host.** The agent of amebiasis is widely distributed in temperate and tropical regions, but the clinical disease is dominantly a feature of the tropics. The character of the human host as influenced by diet is suggested in direct relationship. Faust<sup>25</sup> has stated that probably the most important single intrinsic factor which determines whether amebiasis in a susceptible host is acute, chronic or asymptomatic, is the degree of host resistance based on the nutritional level. Carbohydrate favors multiplication of the agent,<sup>51</sup> and pro-



tein reduces it.<sup>33</sup> The clinical change that takes place when the human host transfers from tropical to temperate regions is as reasonably a function of this social environment-host factor of diet, as of temperature and climate.

**The Need for Quantification.** Hudson<sup>38</sup> has characterized the knowledge of tropical environment as empirical. Many facts are known, much information is suggestively reliable, but all too little has been quantitatively appraised. The preoccupation of students of tropical medicine with the patient<sup>36</sup>—and this has been the white man more than man in general—has led to a highly developed clinical bedside knowledge, to extended descriptions of symptoms and methods of treatment, but too little to the causes of tropical disease<sup>35</sup> as they are determined by age, sex, sanitary environment, local customs and other factors of host and environment. An understanding of the epidemiology of a disease as a community or group problem cannot be expected to arise from the selected and biased data of clinics and hospitals. The need is for a study of tropical disease as a whole, of populations and their reactions.

Epidemiology is thus presented the problem of determining the prevailing influence of environment factors on a communicable disease, in order first to explain the prevailing differences at a given time and secondly the change in places attacked according to time in the same district; and from that knowledge to develop a basis for control. Extraordinarily slight changes<sup>79</sup> in mutual adjustment between host and parasite may profoundly alter clinical and epidemiologic manifestations. The strategy of disease control is often achieved by ecologic measures,<sup>72</sup> to the extent that a newly recognized environmental feature has cleared up problems hitherto entirely obscure.

The need is for precise quantitative information in substitution for impression, suggestion or qualitative fact. It may be sought in two areas.

First, there is a basic need in tropical epidemiology for better information of the movements of disease, comparable to that of temperate climates and based on the frequency of illness and death according to composition of populations. The vital statistics of tropical regions suffer more than the usual unreliability of the census, incompleteness of reporting, diversity in methods of classification, and the inaccuracy of clinical diagnosis.<sup>33</sup> No more than rough estimates must often serve for administrative action. The success or failure of measures introduced in the interests of the public health is to be measured only through the aid of population data, by which trends and tendencies may be expressed in terms of natality, morbidity and mortality. It is obviously unfair that mortality records serve alone, especially when generalization is required from such insecure data as arise from hospital populations.

The second need is a study of host and environment with a care and precision equal to that devoted to the agents of disease. All the elements of environment are not universally and evenly active as an influence on disease. There is an effective and non-effective environment<sup>2</sup> but the distinction is more a matter of degree than of kind. This requires measurement. Well controlled specific quantitative observations on the physiologic effects of the physical environment are few. The social and psychologic effects of the tropical environment have yet to be studied objectively in appreciable population groups, in spite of the evident relationship to economic<sup>88</sup> and industrial<sup>22</sup> development and wholly aside from disease, yet intimately associated with it.

**Specific to the General.** Environment has been analyzed as an influence on communicable disease in groups of people under tropical conditions. The examples given show similar situations to exist among diseases of animals. Etiologically identical processes are observed in both man and other species, sometimes in a goodly number of other species. Often they are epidemiologically so interwoven that an understanding of one is essential to interpretation of the other. The counterpart of such a situation can be identified with ease among diseases of plants. The three components of the tropical environment, distinguished as physical, biologic and socio-economic, are not a particular function of mass communicable disease of man, but are basic to the interpretation of all plant, animal and human infections of those areas.

The part of environment in determining the clinical nature and the distribution of communicable disease is likewise no special attribute of tropical regions. The same qualitative features of environment act on communicable diseases of other climates and other geographical areas. Quantitatively, one or other factor may have altered significance; for example the biologic environment in temperate zones, because of the lesser importance of arthropod vectors in the general scheme. The suggested pattern for the study of environment is believed equally applicable to epidemiologic problems of temperate and polar regions.

The interpretation and analysis of communicable disease as an ecologic phenomenon—the reaction of an organism to its total environment—has as general application to the infectious processes of one region as to those of another. The relationships in some situations may be more complex or more numerous, but basically they conform to principle.

This review has been purposely limited to communicable diseases and the tropical environment but with no suggestion that these conditions are the sole medical problems of the tropics. Time was when they did dominate all considerations. Gradually, if indeed irregularly, the tropics make progress towards conditions characteristic of countries of the temperate zone, where metabolic and degenerative diseases rank higher as judged by death, defect and disability.

An epidemiologic approach to the group or community problems provided by these non-communicable diseases, is as useful as with the infectious processes. Cancer, diabetes, traumatic accidents and heart disease as they affect communities of people are being subjected to such analyses. The same ecologic interpretation can be applied, when the agent is of other nature than a living biologic entity.

The tropical environment may well be examined as an influence on cancer of those regions, especially the physical component of environment; in relation to the intriguing problems of hypertension; and usefully indeed in better appraisal of the socio-economic environment as a determinant of tropical disease of whatever nature.

**Summary.** Each of the factors of environment—physical, biologic and socio-economic—has been considered individually as it acts on the host and on the agents of disease, to the end of demonstrating principle. But the illustrations themselves and more particularly the definition of epidemiology as medical ecology, show this to be an oversimplification. All environmental factors are intimately interwoven, each influenced by the other. The production of disease in man is the resultant of the total forces within a universe, of an ecologic unity.

The principal advances in tropical medicine have been in clinical knowledge of the diseases there present, of the agents responsible and of the vectors involved. These are parts of a broader problem. The fuller understanding of disease in the tropics would seem to require more stress on the study of these conditions as mass disease phenomena, in respect to herd

reactions, having as an objective that epidemiologic interpretation so largely accomplished for disease of temperate regions. The pattern has been set by studies on malaria and yellow fever. The approach is logically that of ecology, in terms of host, agent of disease and environment, with environment of a greater consequence in tropical medicine than under most circumstances.

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# BOOK REVIEWS AND NOTICES

**DISEASES OF CHILDREN'S EYES.** By JAMES HAMILTON DOGGART, M.D. (Cantab.) F.R.C.S. Eng., Ophthalmic Surgeon, Hospital for Sick Children, London, etc. Pp. 288; 210 ills., 32 in color. St. Louis: C. V. Mosby, 1947. Price, \$10.00.

This book was written with the intention of arousing wider interest in the ophthalmic problems of childhood. While the author has succeeded in bringing together enough material to stimulate one's interest, the book fails to be a source of information for those who would seek here what they cannot find in any ordinary textbook. It is too bad that so much space has been taken up with material which should have been assumed to be already part of the reader's general knowledge. The author could have better used this space to give us the benefit of his own experience, which has been large and valuable.

The various forms of glaucoma affecting children are treated on 2½ pages, and the only reference to buphthalmia given in the index is a single line on 1 page. Retino blastoma, surely, should be given comprehensive treatment, but the information supplied here is less than that found in average textbook on ophthalmology.

On the whole, the book falls far short of its purpose because the author has failed to limit himself to his primary endeavor.

F. A.

**PHYSICAL MEDICINE IN GENERAL PRACTICE.** By WILLIAM BIERMAN, M.D., Attending Physical Therapist, Mount Sinai Hosp.; Asst. Clin. Prof. of Medicine, Columbia Univ. With a chapter on Medical Rehabilitation by SIDNEY LICHT, M.D.; 2nd ed. Pp. 686; 310 ills. New York: Paul B. Hoeber, 1947. Price, \$8.00.

THE comprehensive view of the field of Physical Medicine presented in this book gives it value as a reference work for students and practitioners of Physical Medicine. It is commendable, too, that a chapter on medical rehabilitation has been included. The illustrations of the techniques used are well done. On the other hand, since both editions of this book include practically all techniques ever used in Physical Medicine, regardless of their proven value, it seems not well suited for use by the general practitioner, whose limited knowledge in this field makes

discrimination between good and poor techniques difficult. Also, if indications and contraindications for various treatments were given in a more concise form, the book would have more value. The author tacitly recommends by inclusion in the book, the "Knott Ultra Violet Irradiation of Blood", which has not been considered acceptable by the National Research Council and the Council on Physical Medicine of the American Medical Association. The chapter on spa therapy is over-enthusiastic. The author has not stressed sufficiently the potential danger of fever therapy in inexperienced hands. It seems, too, that the terminology of the diseases mentioned would better conform with the Standard Nomenclature of Disease.

J. H.

**ENTWICKLUNGSGESCHICHTE DES KRANKHEITS-BEGRIFFES.** VON DR. EMANUEL BERGHOFF. 2nd ed. Pp. 201. Wien: Wilhelm Maudrich; New York: Grune & Stratton, 1947. Price, \$5.00.

THIS history of the development of the concepts on the nature and causality of disease is essentially a compendium, in which the relevant data, to be found in the standard histories of medicine, have been judiciously and competently abstracted and collated. The work is devoid of originality. It does, however, afford, as the fuller histories do not, a survey and encompassing view of this most important subject. For it is correct, as the author writes in his preface to the second edition, that the *concept of disease* is an indispensable component of medical thought; and that it has a profound influence upon medical practice and research.

The author traces the changing pattern of the concepts of disease from the pre-Hippocratic era down to our time. His treatment of the controverted periods and personalities—the Middle Ages, the Renaissance, Paracelsus, Mesmer, Stahl, the Vienna School—is always understanding and sympathetic. He is very well versed in his subject, and warmly catholic in his sympathies. He is, however, not so well-versed in, nor so judicious in, his treatment of the contemporary scene. The author makes no mention of the British and American writers who have contributed so appreciably to this subject—Major Greenwood, Charles Creighton, F. G. Crookshank, E. W. Goodall, Sir William Hamer and John A. Ryle. Nor is

his treatment of social medicine—the concluding chapter of his work—at all creditable. He makes no mention of the Nuffield Foundation or the Institute of Social Medicine, Oxford University. However, he does dilate on the health services of the U.S.S.R., and celebrates Yugoslavia for “its heroic efforts on behalf of its workers.” I. G.

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MEDICAL CLINICS OF NORTH AMERICA, Boston Number, September 1947. *Specific Methods in Treatment*. Pp. 1059-1319. Phila.: W. B. Saunders, 1947. Price, \$16.00 a year.

THIS symposium summarizes briefly, but adequately, recent thinking as regards the treatment of such common problems as Bright's Disease, meningitis, hypertension, bleeding peptic ulcer, common skin diseases, pernicious anemia, leukemia, toxemia of pregnancy, epilepsy and congestive heart failure. The current status of neostigmine, histamine and histaminase in therapy is discussed. The chapters on the office approach to psychoneuroses, on treatment in child psychiatry and on physical medicine are interesting and useful in themselves. Further, they emphasize that all modern treatment is not by drugs. This is a timely and well selected group of articles, of value to every practicing physician. B. D.

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NEUTRON EFFECTS ON ANIMALS. By the STAFF of the BIOCHEMICAL RESEARCH FOUNDATION, Newark, Delaware. ELLICE McDONALD, M.D., Director. Pp. 198; 29 ill. Balt.: Williams & Wilkins, 1947. Price, \$3.00.

THE volume, a preliminary report of work undertaken in cooperation with the Manhattan District, consists of a collection of observations of various investigators, related to one another in a general way only. They are presented in the same style and form as used in medical periodicals. Despite the title, the experimental organisms employed include corn seedlings and euglena as well as the usual experimental mammals. The presentation consists of a collection of the elementary facts regarding the effects of neutrons on the living organism with no premature attempt to explain mechanisms. The varied problems studied include alterations in blood proteins, resistance to infection, blood cells, and tissue histology resulting from neutron irradiation. Although no correlation of the various endeavors is made and no conclusions drawn, it is of interest to note the compatible results obtained by the various investigators. For

example, it was found that neutron irradiation reduced the number of circulating lymphocytes, reduced the concentration of gamma globulin in the serum, and reduced the resistance of the organism to infection. The volume should be of value at least to those who are working in the field. A. R.

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EAR, NOSE AND THROAT. By GEORGE D. WOLF, M.D., Asst. Clin. Prof. of Otolaryngology, New York Med. Coll. Pp. 523; 149 ill. Phila.: J. B. Lippincott, 1947. Price, \$10.00.

AS A refreshing innovation in this presentation of the fundamentals of otolaryngology, the major portion of this textbook is given to discussions based upon symptom diagnosis and symptoms rather than upon diseases. From this practical approach the various clinical entities are developed and dealt with from the standpoint of etiology, symptomatology, diagnosis and treatment.

PART I deals with the nose, throat and larynx. Specific and concise directions are given for the management of emergencies. The regional subjects are considered from the viewpoint of symptoms—head pain, vertigo, obstructed nasal breathing, postnasal drip, sore throat, obstructive dyspnea and hoarseness. PART II, on the ear, discusses earache, chronic otorrhea, impaired hearing and tinnitus aurium. Other conditions met in otolaryngology such as swelling of the salivary glands, excessive lachrymation and miscellaneous complaints are treated in Part III. Facial plastic surgery is presented in Part IV, while Part V deals with related subjects such as—barotrauma, allergy, blood dyscrasias, avitaminosis and antibiotics. An appendix discusses the planning and equipping of an office.

THE wide teaching experience of the author is reflected in his clear, concise, well-organized text, the courageous elimination of controversial and traditional material, the careful preparation of the instructive illustrations and the insertion of a well-classified, up-to-date bibliography for each subject. Historical notes and clinical anatomy and physiology are introduced without the intrusion of irrelevant information. Wherever emphasis has been deemed necessary illustrative case histories are used. Stress is laid upon the practical aspects of otolaryngology and non-surgical treatment rather than upon surgical techniques. The format and typography of this book are excellent and the arrangement of contents and index such as to permit rapid access to a maximum of information condensed into a minimum of text. The student, gradu-

ate student, teacher and practitioner will find this volume indispensable for rapid reference, basic instruction, authoritative guidance in therapy and bibliographic information.

H. S.

**CALCIUM AND PHOSPHORUS IN FOODS AND NUTRITION.** By HENRY C. SHERMAN, Ph.D., Mitchell Prof. Emeritus of Chemistry, Columbia Univ. Pp. 176. New York: Columbia University Press, 1947. Price, \$2.75.

THIS small volume presents a concisely written summary of our present knowledge of calcium and phosphorus in relation to nutrition. A short introduction explains the place of these two elements in nature, in our agricultural economy and in human nutrition. Five topics are then considered: the calcium in the body, especially its forms and function in the blood and the bones; the effects of foods and of growth upon the calcium content of the body; a summary of the chemical forms and nutritional functions of phosphorus; a review of the evidence upon quantitative requirements with particular reference to minimal adequate and optimal intakes; and foods as factors in providing these two elements and affecting their utilization. A final chapter summarizes and interprets these data in respect to modern nutrition. A selected bibliography of over 600 references serves to document the discussions.

H. V.

**CASE HISTORIES IN CLINICAL AND ABNORMAL PSYCHOLOGY.** Edited by ARTHUR BURTON, Assoc. Prof. of Psychology, Willamette Univ., and ROBERT E. HARRIS, Assoc. Prof. of Medical Psychology, Univ. of California. Pp. 680. New York: Harper & Bros., 1948. Price, \$4.00.

THIS book is by clinical psychologists for clinical psychologists. Much of its space is therefore devoted to the demonstration of the use of psychological tests in the diagnosis, prognosis and treatment of cases ranging from the mental deficiencies to neuroses and psychoses. A main purpose is to supply case material for courses to college students.

A valuable introduction by Henry Murray mentions the acquisition of "certain medical principles and practices by psychologists", and notes that psychologists have never published a set of case records of normal people.

The present collection of case histories of the abnormal will be used to educate the great numbers of new students, many of them veterans, who are preparing themselves for positions in psychology.

E. B.

## NEW BOOKS

*Gazeta Medica Portuguesa.* Editor: PAOLO MARQUES, Rua de Prata, 250-2°, Lisbon. Pp. 250. Lisbon, 1948. Price, \$20.00.

WE ARE glad, contrary to our usual custom, to bring to the attention of our readers this first number of what appears to be an important quarterly journal.

*Pioneer Life in Kentucky, 1785-1800.* By DANIEL DRAKE, M.D. Edited by EMMET FIELD HORNE, M.D. Pp. 257. New York: Henry Schuman, 1948. Price, \$4.00.

THE "reminiscential" letters that comprise this volume were first published in 1870 and again in 1907—both editions are exceedingly rare. Though only indirectly medical, they present a picture composed by the leading early physician of the Mississippi Valley that should especially interest the medical world of this country.

## NEW EDITIONS

*Modern Trends in Ophthalmology.* Edited by ARNOLD SORSBY. Vol. II. Pp. 600; 169 ills. New York and London: Paul B. Hoeber, 1948. Price, \$12.50.

THIS continuation of the first volume of this book published in 1940 consists of 48 short monographs by different authors covering a wide field of subjects of interest to ophthalmologists. The papers are grouped into 5 sections, namely: physiology, diagnostic procedures, pathology treatment, and social aspects of ophthalmology. As is to be expected in a book of this sort some sections are better prepared than others but, on the whole, the high standard of the first volume is maintained.

F. A.

*A Textbook of Clinical Pathology.* Edited by FRANCIS P. PARKER, M.D., Assoc. Prof. of Pathology, Univ. of Virginia School of Medicine. 3d ed. Pp. 1023; 229 ills. Balt.: Williams & Wilkins, 1948. Price, \$9.00.

THIS new edition contains a valuable store of details and interpretations of laboratory tests. Sections on the various aspects of clinical pathology are written by different authors, most of whom are leading investigators in their field. Among the subjects considered are practically all aspects of hematology, serologic tests for syphilis, immunologic tests, liver function, assay of vitamins and hormones, blood chemistry, and examination of sputum, feces, spinal fluid, urine, gastric contents and seminal fluid. The illustrations are numerous and clear, and the book is replete with new developments in laboratory technique and tests.

I. Z.

*Die Lungentuberkulose beim Erwachsenen.* Von DR. HERMANN WEBER. 2d ed. Pp. 417; 248 ills., 11 in color. Wien: Maudrich, 1948. Imported by Grune & Stratton. No price given.

*Essentials of Fevers.* By GERALD E. BREEN, M.D., Examiner in Fevers to the General Nursing Council of England and Wales. 2d ed. Pp. 351, 16 ills. Balt.: Williams & Wilkins, 1948. Price, \$4.50.

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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## ORIGINAL ARTICLES

### CHRONIC CONSTRICTIVE PERICARDITIS A STUDY OF 53 CASES

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(From the Massachusetts General Hospital)

SINCE 1914, 53 cases of chronic constrictive pericarditis have been seen at the Massachusetts General Hospital and in the private practice of one of us (P.D.W.). Some of these cases have been described in previous publications.<sup>3,7</sup> With the addition of new case material, it seemed wise to review our experience, both to analyze more closely the clinical picture and to evaluate the long-term results of surgery. In addition we have summarized for the first time the pathological findings on those patients who succumbed to the disease or to its complications and on whom autopsy data are available.

The patient who complains of shortness of breath, increase in girth, and swelling of the ankles, who shows prominence of the neck veins, hepatomegaly, and peripheral edema, and

yet has a quiet and often normal-sized heart may offer a puzzling diagnostic problem. A high index of suspicion is needed in these patients with unexplained heart failure or with atypical cirrhosis of the liver, if the diagnosis of constrictive pericarditis is to be made. The absence of clearcut evidence of other types of heart disease, the helpful Roentgen-ray pictures, and the more or less characteristic electrocardiographic pattern are the most valuable clues. As we have become familiar with the effects of cardiac constriction it has been easier to detect these cases. Despite the most careful studies, however, the etiology still remains obscure in many instances, the diagnosis sometimes difficult, and the treatment far from a simple matter. It should be emphasized that except in very mild cases the disease is a serious



one, carrying with it a considerable disability and mortality, notwithstanding the encouraging advances in surgical treatment.

1. Clinical Data Concerning Our 53 Cases. A. *Sex.* There were 36 males (67.9%) and 17 females (32.1%) in the series.

B. *Age of onset of symptoms of chronic constrictive pericarditis.* The number of cases for each age group is indicated in Table 1.\* Our youngest

at the onset. (These are indicated in Chart 1.) Dyspnea on effort was by far the most common initial complaint, being followed in order by swelling of the ankles and shins, abdominal swelling, palpitation, and weakness. The lack of breathlessness in cases of constrictive pericarditis has sometimes been a matter of comment, but it is obvious from this analysis that the patients themselves were aware of a definite diminution in their exercise

TABLE 1.

AGE AT ONSET OF SYMPTOMS OF CHRONIC CONSTRICTIVE PERICARDITIS  
(52 Cases)

Age in Years	Number of Cases	% of Total
0-9 years	1	1.9
10-19 years	13	25.0
20-29 years	13	25.0
30-39 years	11	21.1
40-49 years	7	13.5
50-59 years	7	13.5

TABLE 2.

DURATION OF SYMPTOMS OF CHRONIC CONSTRICTIVE PERICARDITIS  
(prior to first visit to us)

Years	Number of Cases	% of Total
0 (no symptoms)	1	1.9
0-1	18	33.9
2-4	19	35.8
5-9	10	18.9
10-19	3	5.7
20-29	2	3.8

patient became ill at the age of 16 months and our oldest at the age of 58 years. Over 70% of the group were between the ages of 10 and 40 years.

C. *Duration of symptoms of chronic constrictive pericarditis prior to first visit to us.* (These figures are to be found in Table 2.) 65% of the patients had noted symptoms for 2 years or more. The longest total duration of symptoms has been 44 years.

D. *Initial symptoms.* It is of interest to ascertain what symptoms were first troublesome. In some cases, 2 or even 3 symptoms appeared together

tolerance. Orthopnea as an initial symptom was found, however, only three times.

E. *Symptoms when first seen by us.* (Chart 1 also lists all symptoms which were mentioned by the patients when interrogated on their first visit to us.) It will be seen that these are very similar in their incidence to those causing complaint at the onset of the disease, although orthopnea is found with increasing frequency. Again, shortness of breath on effort was the outstanding complaint. Investigation of the group of patients who were

\* We have not included in Table 1 one patient, aged 23 years, who was symptom-free despite clear evidence of pericardial constriction.

dyspneic (41 cases) as contrasted with the smaller group of patients who were not (12 cases) shows an almost identical incidence of unilateral and bilateral pleural effusions (as found by Roentgen-ray), ascites, and auricular fibrillation or flutter. It would therefore appear that shortness of breath is not necessarily

the result of a reduction in the lung volume secondary to hydrothorax or a high diaphragm, or to the presence of a cardiac arrhythmia, but is consequent to a reduced pulmonary blood flow, or to congestion in the pulmonary circulation, resulting from cardiac tamponade.

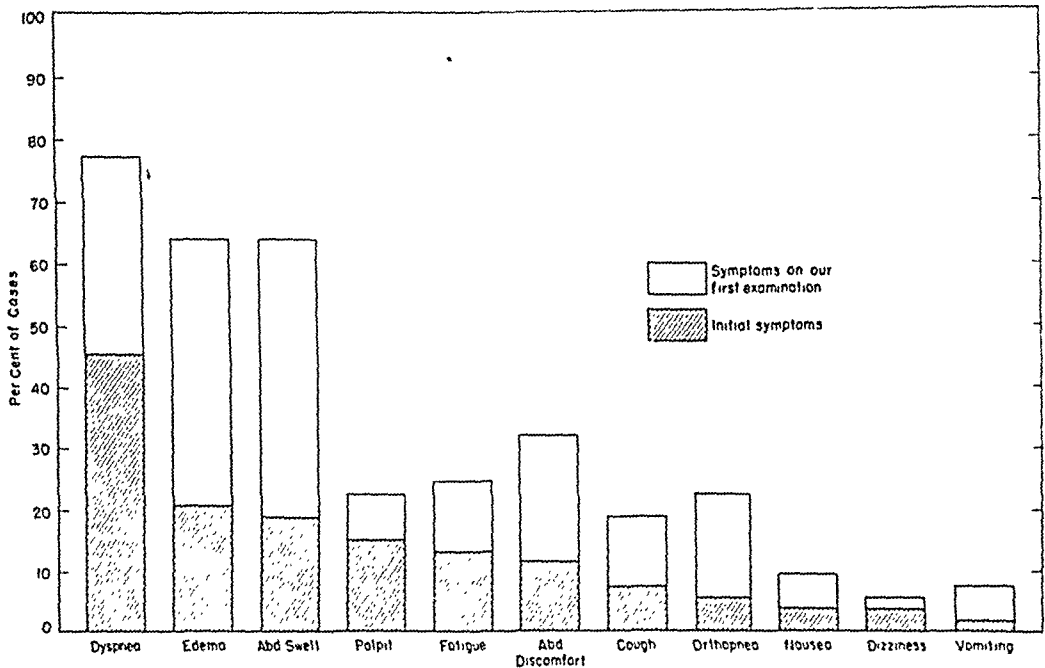


Chart 1. Symptoms (53 Cases)

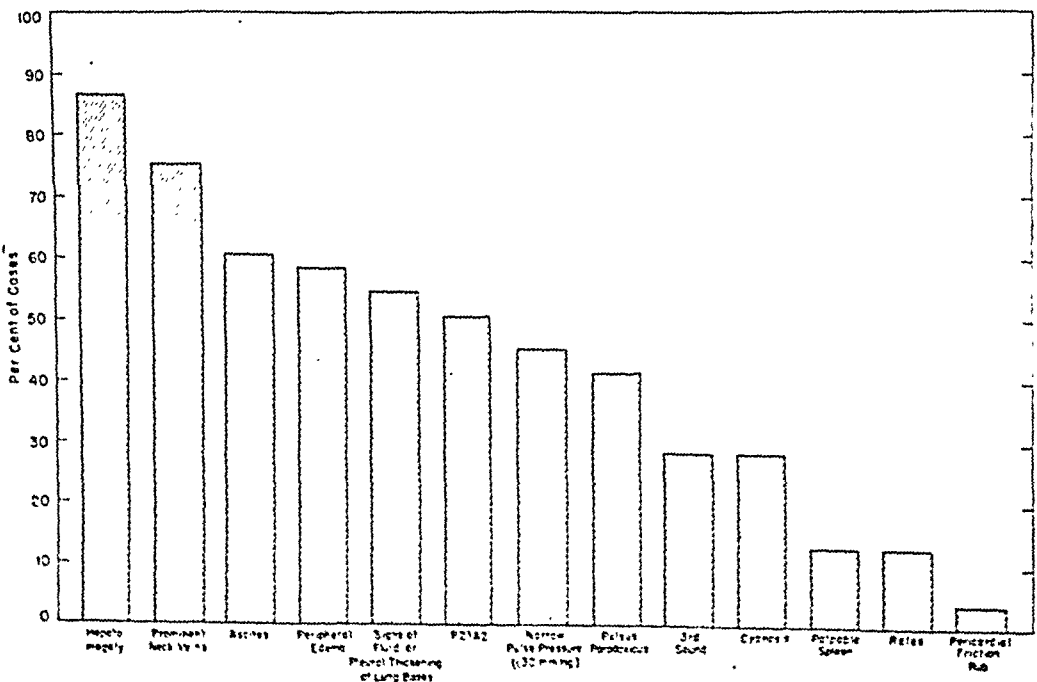


Chart 2. Physical Findings (53 Cases)

*F. Physical findings when first examined.* An enlarged liver was the commonest finding, and the actual incidence of hepatomegaly is undoubtedly higher than is indicated on Chart 2, due to the fact that liver enlargement could not be demonstrated where marked ascites was present. Prominence or pulsation of the cervical veins (with the patient in the erect position) was noted in 75% of the patients but was probably present, in minor degree at least, in the remainder. Ascites, peripheral edema, and signs of pleural fluid or pleural thickening were found in the majority. The fact that approximately half of the patients were observed to have an accentuation of the second sound in the pulmonic area is a significant physical finding, both in view of the incidence of dyspnea and the relatively few (22%) who were under 20 years of age when examined. It suggests the importance of left, as well as right, ventricular constriction. Another interesting auscultatory finding was the presence of a distinct third sound at the apex or at the lower left sternal border, or at both areas, in 15 of the cases. Slightly less than half of the group showed narrowing of the pulse pressure (and this was marked in only 4 patients) or pulsus paradoxicus. Uncommon were râles in the lung fields, splenomegaly, and a pericardial friction rub.

No consequential murmurs were noted, except in 3 patients. A loud apical systolic murmur was heard in 2 patients, 1 of whom showed aortic stenosis at autopsy. In a third patient a loud systolic murmur was found in the fourth intercostal space along the left sternal border and was accompanied by a systolic thrill; at first this was thought to be typical of an incidental interventricular septal defect, but of late it has become much less loud and is now considered to be of doubtful significance.

*G. Heart size.* Determination of the heart size by physical examination was unreliable, due to the frequency of pleural thickening and effusion and because of the feeble character of the apex impulse. Roentgenographic observations were made on admission in each case, however, and revealed a normal cardiac shadow in 24 patients (45.2%), a slight increase in size in 9 (17.0%), a moderate enlargement in 17 (32.1%), and a greatly enlarged heart in only 3 (5.7%).

*H. Incidence of calcification in the pericardium.* Calcium was demonstrated to be present in the pericardium by Roentgen-ray study, observations at the time of operation, or postmortem examination in 29 of the 53 cases (54.7%).

*I. Cardiac pulsations as observed by fluoroscopy.* No information is available on the character of the pulsations of the heart in 13 patients (24.5%). In 26 patients (49.0%) fluoroscopy at the time of admission revealed a definite diminution of the pulsations of the heart, at times limited to one border, and in 6 patients (11.3%) there were no cardiac pulsations visible. It is very important to note that in 8 cases (15.2%) normal excursions of the heart were described.

*J. Incidence of hydrothorax.* Chest Roentgen-ray films disclosed that pleural fluid was present in 28 of the 53 cases (52.8%). This was limited to the right pleural cavity in 11 patients, was confined to the left pleural cavity in 3 patients, and was bilateral in 14.

*K. Electrocardiographic findings.* Electrocardiograms were available on 52 of the 53 patients in the series. The rhythm was normal throughout in 32 of these (61.5%). In the remaining 20 patients (38.5%) abnormalities consisting of auricular fibrillation (18 cases) or of auricular flutter (5 cases, in 3 of which auricular fibrillation was also noted) were present as follows:

auricular fibrillation, apparently permanent (6 of these cases were operated upon) . . . . .	12 cases
auricular fibrillation with one transient reversion to normal rhythm (no operation performed) . . . . .	1 case
normal rhythm followed by apparently permanent auricular fibrillation (no operation performed) . . . . .	2 cases
normal rhythm followed post-operatively by auricular flutter, then fibrillation, apparently permanent . . . . .	1 case
auricular flutter followed post-operatively by auricular fibrillation, apparently permanent. . . . .	2 cases
auricular flutter, apparently permanent (surgery performed) . . . . .	1 case
auricular flutter, transient, post-operative only . . . . .	1 case

It will be observed that in no instance was partial resection of the pericardium followed by normal rhythm when an arrhythmia existed prior to operation. It is also of interest that the 32 patients whose rhythm was normal at the time of admission had been having symptoms for an average period of only 2.8 years, whereas the 15 patients whose rhythm was abnormal on admission and remained so had an average duration of symptoms of 7.4 years. The rhythm was described as clinically normal in the one patient who had no electrocardiogram recorded.

The height of the greatest QRS complex in the limb leads was no greater than 3 mm. in 17 cases (32.6%); left axis deviation was found twice and right axis deviation only once. The T waves in all the limb leads were low, flat, or inverted in 45 patients (86.5%). These figures call attention again to the importance of the electrocardiographic pattern of low voltage,

and flattening of the T waves with or without auricular fibrillation, as an extremely valuable clue in the diagnosis of chronic constrictive pericarditis. This point was well demonstrated in one of our own patients on whom various other diagnoses had been entertained until the electrocardiogram directed attention to a constricting pericardium as the underlying disease process.

*L. Other laboratory findings.* The venous pressure was determined in 36 of the patients, using the intravenous method, and was found to be greater than 150 mm. of water in 33; the readings were 110, 130, and 140 mm. of water respectively in the remaining 3 cases, still suggesting elevated readings. A significant anemia (less than 75% hemoglobin or 4 million red cells per cubic millimeter) was uncommon, being present in but 9 out of 51 patients on whom such hematological data are available. The total serum protein was assayed in 38 cases and was normal in 20, high (10.2 gm. per 100 cc.) in 1, and low (less than 6.0 gm. per 100 cc.) in 17. The albumin/globulin ratio was found to be definitely low (less than 1.2) in 4 out of 17 determinations.

**2. Results of Surgery.\*** Surgical exploration with pericardiolysis and partial pericardiectomy was undertaken on 42 patients, 36 of whom were operated upon only once. Five patients were operated upon twice because of failure of the first procedure to improve their clinical status satisfactorily, and one patient has been operated upon three times. An anterior or anterolateral precordial incision was used in all cases, with the exception of one case in which a posterolateral incision was employed.<sup>8</sup>

\* The first pericardiolysis and partial pericardiectomy in this series was performed in July 1928 by Dr. Edward D. Churchill, and he and Dr. Richard Sweet are together responsible for the gratifying results obtained in these cases.

Truly remarkable recoveries were made in 15 of the 42 patients thus operated upon, and they are regarded as having been essentially cured of their symptoms. Table 3 indicates the extent of this striking transformation, including the disappearance of all disabling symptoms and of almost all abnormal physical findings.

Another group of 10 patients showed definite improvement following operation: 8 are living, and 2 died six years following pericardiectomy. That surgery was of benefit to them is unquestioned, and, as may be seen in Table 4, their symptoms were ameliorated and the effects of pericardial constriction diminished.

There is one additional patient whose last operation took place less than 1 year ago. Although he is doing well, we have not included him in our follow-up figures, as we need a longer period of postoperative observation for accurate appraisal. The surgical approach in his case was unusual and has been made the subject of a separate report.

Satisfactory or excellent results have thus been obtained in 25 (60.9%) of the patients coming to operation.

Of the remaining 16 patients (Table 5), 6 died as the result of the operative procedure itself. Three of these succumbed on the operating table, 1 died one day postoperatively with pulmonary edema, 1 died of pulmonary embolism on the second postoperative day (he is the only case included in the series who was operated upon at another hospital), and 1 of bronchopneumonia and pulmonary edema 6 days after surgery.

Another group of 5 cases demonstrates death from complicating diseases. All survived the immediate effects of pericardiectomy but died from 1 month to 2 years later of illnesses which included acute pancreatitis,

arterial embolism (following an omentopexy), empyema, pneumonia, and widespread sepsis. Four other patients died from 4 to 9 months after their operations from the effects of their underlying disease. The cause of death of 1 other patient, who died in another city 2 months after pericardiectomy, is not known.

**3. Status of Patients Not Operated Upon.** Seven patients were thought to be too ill for surgery, and all were treated medically in the hope that their clinical condition might improve to the point where the risk of operation was reasonable. All of these patients are now dead, a few months to 12 years after we had first examined them. Two of these were proved to have tuberculosis and the other 5 died in congestion.

The effects of the constrictive pericarditis were so minimal in 2 patients that surgery was thought to be unnecessary. One of these patients had mild symptoms for over 50 years and finally succumbed at the age of 76 (he has been reported extensively in a previous publication<sup>3</sup>); while the other had until recently been only mildly inconvenienced by the presence of palpitation secondary to auricular fibrillation.

One patient died in congestion before the operative series began, and another patient could not be traced.

**4. Pathological Studies.** A review of some of the findings at operation, as well as of the gross and microscopic findings on the 16 autopsied cases, throws considerable light on the extent of the pathological changes, the variety of tissues involved, and some of the reasons why surgical removal of portions of the anterior and anterolateral portions of the pericardium failed at times. It is to be remembered that these data come largely from the most severe examples of the disease.

TABLE 3. STATUS OF PATIENTS ESSENTIALLY CURED BY SURGERY

Case P.C.	Follow-Up Period (years)	Symptoms		Prominent Neck Veins		Liver Size		Edema		Ascites		Lungs		Present Activity
		Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	
J.K.	3	Dyspnea; edema; Abdom. discomfort	None	+	0	Enl.	Normal	+	0	0	0	Rt. hydro- thorax	Normal	Normal life
E.B.	2	Dyspnea Abdom. discomfort	None	+	0	Enl.	Normal	0	0	0	0	Bilat. hydrothorax	Normal	Normal life
R.C.	1	Orthopnea; abdom. swelling; edema	None	0	Sl. dist	?	Normal	0	0	0	0	Bilat. hydrothorax	Normal	Normal life
T.P.	3	Abd. discomfort and swelling	None	+	0	Enl.	Normal	+	0	0	0	Rt. hydro- thorax	Normal	Normal life
A.T.	5½	Orthopnea; abdom. swelling; edema	None	+	0	Enl.	Normal	+	0	0	0	Bilat. hydrothorax	Normal	Normal life
F.S.	3	Palpitation; edema; abdom. discomfort	Some palpitation	+	0	Enl.	Normal	+	0	+	0	Rt. hydro- thorax	Normal	Normal life
C.O.	4½	Dyspnea; emesis; abd. swelling; edema	None	+	0	Enl.	Normal	+	0	+	0	Rt. hydro- thorax	Normal	Normal life
B.K.	18½	Orthopnea; abdom. swelling and discom- fort	None	0	0	Enl.	Normal	0	0	0	0	Normal	Normal	Normal life
L.L.	12½	Dyspnea Abdom. swelling	None	+	0	Enl.	Normal	0	0	0	0	Normal	Normal	Normal life
A.F.	13	Dyspnea; abdom. swelling; edema	None	0	Sl. dist.	Enl.	Sl. enl.	+	0	+	0	Bilat. hydrothorax	Normal	Normal life
L.C.	13½	Dyspnea; abdom. swelling; edema	None	+	0	Enl.	Sl. enl.	0	0	0	0	Bilat. hydrothorax	Normal	Normal life
S.L.	13½	Abd. swelling	None	+	0	Enl.	Normal	+	0	+	0	Normal	Normal	Normal life
H.W.	5	Cough; edema	None	+	0	Enl.	Normal	+	0	+	0	Normal	Normal	Not known
R.R.	6½	Dyspnea; abdom. swell- ing and ache; edema	None	+	0	Enl.	Normal	+	0	0	0	Normal	Normal	Normal life
	1½	Nausea; emesis; leg pain; edema	None	+	0	Enl.	Normal	0	0	0	0	Normal	Normal	Normal life
				+	0	Enl.	Normal	0	0	+	0	Normal	Normal	Normal life
				+	0	Enl.	Normal	0	0	0	0	Rt. hydro- thorax	Normal	Normal life
				+	0	Enl.	Normal	0	0	0	0	Pleur. thick. rt. base	Normal	Normal life
				+	0	Enl.	Normal	0	0	0	0	Dry Rales rt. base	Normal	Normal life
				+	0	Enl.	Normal	0	0	0	0	Normal	Normal	Normal life

\* No data available.

TABLE 4. STATUS OF PATIENTS IMPROVED BY SURGERY

Case	Follow-Up Period (years)	Symptoms		Prominent Neck Veins		Liver Size		Edema		Ascites		Lungs		Present Activity
		Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	
D.G.	11	Fatigue Abdominal swelling and discomfort	Sl. dyspnea	+	+	Normal	Normal	0	+	0	Normal	Normal	Normal	Sedentary job
G.P.	6	Dyspnea Abdominal swelling	Some dyspnea	+	+	Enl.	Normal	+	+	?	0	0	0	Limited activity until death 6 yrs. later
P.C.	8	Abdominal swelling and discomfort	Sl. dyspnea Palpitation	+	+	Sl. dist.	Enl.	0	Sl.	+	0	Bilat. hydrothorax	Normal	Normal life
W.R.	6	Dyspnea; palpitation; abdominal discomfort	Sl. chest discomfort	0	0	Enl.	Enl.	0	0	0	0	Normal	Normal	Normal life
M.C.	3	Orthopnea Abdominal swelling Edema	None	+	+	Sl. dist.	Enl.	+	0	+	0	Bilat. hydrothorax	Left hydrothorax	Normal life
M.W.	1	Dyspnea; abdominal swelling and discomfort; edema	Some dyspnea	+	+	Dist.	Enl.	0	0	+	0	Left hydrothorax	Normal	Limited activity
E.F.	3½	Dyspnea Abdominal swelling and discomfort	Palpitation Sl. edema	*	Dist.	Enl.	Normal	+	0	+	0	Bilat. basal rates	Normal	*
E.M.	3½	Orthopnea Abdominal swelling and discomfort	Sl. dyspnea	+	+	*	Enl.	+	0	0	*	Bilat. hydrothorax	Normal	Normal life
A.J.	1½	Orthopnea Abdominal swelling Edema	Some edema	0	0	Sl. dist.	Enl.	0	Sl.	0	0	Rt. hydrothorax	Normal	Limited activity
O.P.	6	Dyspnea Abdominal swelling Edema	None while followed	+	+	Enl.	*	+	+	+	*	Rt. hydrothorax	*	Limited activity until death from pneumonia 6 yrs. later

\* No data available.

TABLE 5. STATUS OF PATIENTS UNIMPROVED OR ONLY TEMPORARILY BENEFITED BY SURGERY

Died on operating table (during first operation)	2
Died on operating table during second operation (status not materially improved by first operation)	1
Died in pulmonary edema 1 day postoperatively	1
Died of pulmonary embolism 2 days postoperatively	1
Died of bronchopneumonia and pulmonary edema 6 days postoperatively	1
Died of acute pancreatitis 1 month after second operation	1
Died of general sepsis 1 year postoperatively	1
Died of arterial embolism following an omentopexy (2 previous partial pericardiectomies had failed to improve his condition adequately)	1
Died of a type III pneumococcal empyema 1 year postoperatively, the symptoms and signs of cardiac tamponade having been much improved temporarily	1
Died of bronchopneumonia 2 years postoperatively, without having benefited significantly from surgery	1
Died 4, 6, and 9 months postoperatively, respectively, in congestion	3
Died 6 months postoperatively, ? due to complicating Addison's disease	1
Died 2 months postoperatively, cause of death not known	1
Total	16

At the time of operation the surgeon observed evidence of an active inflammatory process in the pericardium in 6 cases (the total number coming to surgery was 42). The note on one such patient mentions that "there were multiple small bleeding points and the entire surface of the heart presented the appearance of a subacute inflammatory process." In another instance the situation was complicated by "edema and rather recently appearing inflammatory reaction which fused the pleura and pericardium together . . . the pericardium was very adherent and the adhesions were much more vascular and a cleavage plane less easily found than in the average case of longer duration. . . ." Similar remarks were made in the records of 4 other patients. It is interesting that 4 of these 6 cases are now thought to have been cured by operation, and 1 has improved although 2 operations were required for relief.

The typical findings in the pericardium at operation on the other cases were those of extensive old fibrosis and scarring. The pericardium was thickened and tough and, as noted previously, at times contained calcium deposits; and the pericardial cavity in so far as it could be examined was usually obliterated. On resection of a portion of this constricting envelope, the surgeon often observed that the released auricles and ventricles filled

more fully. It is clear that much of the epicardium, as well as the pericardium, was removed in certain cases, both because the two membranous layers were so fused that a plane of dissection between them could not be found and because removal of the epicardium itself was often a prerequisite to adequate diastolic filling.

Considering the condition of the pericardium as found at autopsy, we discovered that in only 2 instances did small, free, unobliterated pockets of pericardial cavity persist. In the other 14 autopsied cases the pericardial and epicardial surfaces had completely fused. The pericardium was thickened in all cases, the greatest thickness ranging from 3 to 20 mm., and in 11 of the specimens calcification was present. The extent of this calcium deposition is indicated in Table 6. It will be seen that all surfaces were involved in 4 cases, that calcified rings were found in 2, and that the pericardium overlying the chambers of the heart was variably affected in the remaining 5. In particular, the posterior aspect of the left ventricle—an area out of the reach of the surgeon from the anterior approach—was calcified in 8 instances. There was only 1 example of a fibrotic ring constricting the great veins as they entered the heart. It seems apparent from these findings that in some cases of constrictive pericarditis, removal of the anterior or anterolateral



portions of the pericardium alone may be inadequate to release auricular and ventricular action completely.

Another reason why certain patients with this disease may not achieve completely satisfactory clinical results following surgery is to be found in a study of the myocardium itself. In 4 patients the surgeon commented at operation upon the flabby or thin appearance of the heart wall. In 1 of these the

sis was thus produced which probably explained the auscultatory evidence of mitral stenosis observed during life. Microscopic studies of the myocardium showed degenerative changes in 5 of the 16 so studied. Two of these showed relatively slight myocardial fibrosis. An interesting finding in a few of the cases was adventitial and perivascular edema and fibrosis due probably to an extension of the process in-

TABLE 6. EXAMINATION OF THE PERICARDIUM AT AUTOPSY  
(16 Cases)

Thickened pericardium	16
Calcification of the pericardium	11
1) complete	1
2) complete save for operative defect	1
3) "extensive"	1
4) small amount diffusely	1
5) anterior, right lateral, and diaphragmatic surfaces	1
6) entire left ventricle and right auricle	1
7) left ventricle (anterolateral and part posterior aspect) and right ventricle	1
8) posterior aspect left ventricle	1
9) lateral and posterior surfaces of heart	1
10) band around A-V groove	1
11) ring around apex	1
Complete obliteration of pericardial cavity	14
Fibrotic ring around venae cavae	1

friable character of the muscle was graphically described by the surgeon's note, which stated: "I was gently sponging in the depths over the right auricle with a moist cotton pledget in a Hartmann forceps. Suddenly to my horror the forceps plunged into the cavity of the heart and there was a profuse hemorrhage of dark venous blood." The bleeding was controlled, and the patient is now well. In another case the right ventricle was similarly ruptured but was patched with pericardium and the patient survived.

At autopsy it was found that calcification extended into the myocardium itself in 4 instances, in 1 case forming a solid core of calcium through the right ventricular wall appearing on the endocardium, and in the other 3 cases penetrating the left ventricle and impinging upon the mitral valve. In 1 of the latter cases a slight mitral steno-

ward from the thickened visceral pericardium.

The possibility has also arisen that the formation of scar tissue over the defect in the pericardium resulting from the partial pericardiectomy might reproduce the same constriction of the heart that was present prior to operation. There are 4 instances in which such scar tissue found at the time of postmortem examination may have been of significant effect. In 3\* of these, dense fibrous tissue had replaced the area of pericardium which had been removed; in the fourth a moderate amount of scar tissue had formed. Regarding another patient, on whom 2 partial pericardiectomies were performed, the surgeon remarked at the time of the second procedure that "at the lower end of the incision considerable scar tissue bound the heart to the sixth costal cartilage. This was

\* These 3 patients all died from complicating disease, but 2 of them appeared to have received definite benefit from surgery.

resected and in itself appeared to give considerably more freedom to the heart."

There are thus called to mind 4 conditions which may interfere with the success of a pericardiectomy: (1) incomplete removal of constricting pericardial tissue, (2) disease of the myocardium itself, (3) formation of constricting scar tissue over the defect in the pericardium (apparently a relatively insignificant factor), and (4) persistence of an active inflammatory process.

Adhesions extending from the pericardium into the mediastinum and involving the esophagus and other structures were found only twice.

Pleural involvement, with pleuritis at times completely obliterating a cavity, was discovered in 15 of the 16 autopsied cases. This pleuritis was bilateral in 13 and was limited to the right pleural cavity in 2 instances. A bilateral hydrothorax was present in 6 cases, a right hydrothorax in 2, and a left hydrothorax in 3. Active pulmonary tuberculosis was noted only once.

An abnormal liver was a characteristic finding in all 16 of these postmortem examinations. Four of the livers weighed more than 1600 grams, and a perihepatitis was present in nine. In 14 a definite cirrhosis was present and most of these were diagnosed as cardiac in type. Cardiac, or what Koletsky and Barnebee<sup>5</sup> prefer to call "congestive," cirrhosis supposedly results from long standing passive congestion. Although the early changes in this condition are limited to the central areas, varying degrees of portal fibrosis are usually present, accounting for a diagnosis of portal and unclassified cirrhosis in a few of the cases.

Most of the reports dealing with cardiac cirrhosis emphasize that the fibrosis may be limited to the central areas, but that in cases with very long

periods of congestive failure the fibrosis is also portal, and the cases of constrictive pericarditis would fit into this latter group. The usual explanation for the portal fibrosis is that the chronic passive congestion produces anoxemia and thus makes the liver cells anywhere in the lobule more susceptible to injury.

In reviewing the liver sections in this series of constrictive pericarditis cases, it was apparent that portal fibrosis was quite prominent in most of the cases. In a few cases this was most marked in the parenchyma not far from areas of perihepatitis, and it is quite possible that the portal fibrosis is in part due to extension down from Glisson's capsule.

Another factor, and one that has not been emphasized before, although it is probably more important than the above-mentioned considerations, is the finding of marked intimal thickening with luminal narrowing, and in some cases definite thrombosis with recanalization, of the hepatic veins. This endophlebitis process due to long standing high venous pressure must have produced a mild Chiari syndrome leading to portal hypertension, portal fibrosis, and possibly additional ascites. Confirmation of this portal hypertension is found in the presence of splenomegaly in some of these cases. Most of the spleens weighed over 300 grams; three weighed 350, 430, and 600 grams respectively. Since some cases of unquestioned cardiac cirrhosis resulting from valvular heart disease have shown similar hepatic vein changes, it is believed that the cirrhotic changes (whether central or portal) in chronic constrictive pericarditis are the result of chronic passive congestion and can be legitimately called "cardiac" or "congestive" cirrhosis.

A perisplenitis was diagnosed in 9 cases, and there was a chronic peritonitis present in 3.

5. Etiology. In 56.5% of the patients of our series neither the history nor the laboratory studies gave a clue as to the etiology of the disease process. (Sections of the pericardium were available for microscopic study in 46 of our 53 cases.) The characteristic story was one of a gradual awareness of ill-health, coming on over months or years without an acute or otherwise remarkable illness initially. On reviewing the records, not only do we find the past history to be of no assistance but there is no evidence of unusual familial incidence of tuberculosis or rheumatic fever and no reference to close contacts with friends or relatives afflicted with these diseases.

A *tuberculous origin* was demonstrated in 9 patients (17.0%) either by guinea pig inoculation of the pericardial fluid or by pathological study of the pericardium. Three of these patients were females. A pericardiectomy was either performed or attempted on 7 of the 9, with one patient dying on the operating table, 1 dying the day after the procedure, 1 succumbing a month later to a complicating pancreatitis, and 1 dying 2 years later of pneumonia (minimal active pulmonary tuberculosis was present at autopsy also). Three patients are alive and well from 3 to 6 years after surgery. The other 2 patients died after a six month and a 2 year illness respectively, without attempt at operation (1 of these showed miliary tuberculosis at post-mortem examination). Thus 6 of the group are now dead.

This group of 9 cases is too small for definite conclusions, but a few observations on the clinical and pathological findings may be pertinent. It

may be significant that only 2 of these patients had been ill for as long as 2 years when first seen by us, and the others for only a year or less, whereas in the rest of the cases in the series 74% had noted their symptoms for 2 years or more. The infrequency of pericardial calcification and of cardiac arrhythmias is also of interest, these findings being noted only once each (and both in the one patient who had been ill the longest).<sup>\*</sup> By contrast, 38% of the other 44 cases showed auricular fibrillation or flutter and 64% showed a deposition of calcium in the pericardium by Roentgen-ray examination or by pathological study. In only 1 case was there diagnostic evidence of active tuberculosis elsewhere than in the pericardium.

A review of the microscopic findings in the pericardial sections obtained at the time of autopsy or from surgical biopsy specimens from both tuberculous and nontuberculous cases disclosed two additional and important considerations. First, it is obvious that the diagnosis of tuberculous pericarditis may be missed if an inadequate number of tissue sections is studied. In 1 recent case, extensive examination of numerous microscopic sections was required before clear cut evidence of tuberculosis was found. It is not hard to see how failure to select the right portion of pericardial tissue or to take additional sections from tissue blocks may result in a report merely of fibrosis or inflammation and fibrosis. Secondly, there is no sharp dividing line between the microscopic picture of healed tuberculous pericarditis and what may be called idiopathic constrictive pericarditis. In both conditions pericardial

<sup>\*</sup> Since the above was written, another tuberculous case, a 23 year old patient of Dr. Conger Williams, has been seen at the Massachusetts General Hospital. He had been ill for 4 months with evidence of progressive cardiac tamponade and died a few hours after admission to the hospital. Postmortem study disclosed a thickened pericardium which did contain some calcium, and microscopic sections revealed tuberculous involvement of the pericardium and of the mediastinal nodes. No arrhythmia had been observed, and it is of interest that his illness was of such short duration.

fibrosis and at times chronic inflammatory changes with an infiltration of lymphocytes are present. In both, giant cells may be found, related to tubercle formation or to a foreign body reaction due to calcium deposition or to the two together. Figure 1 indicates the microscopic appearance of two areas of the pericardium of a tuberculous case, showing typical tubercle formation on the one hand and nonspecific changes (of the type usually

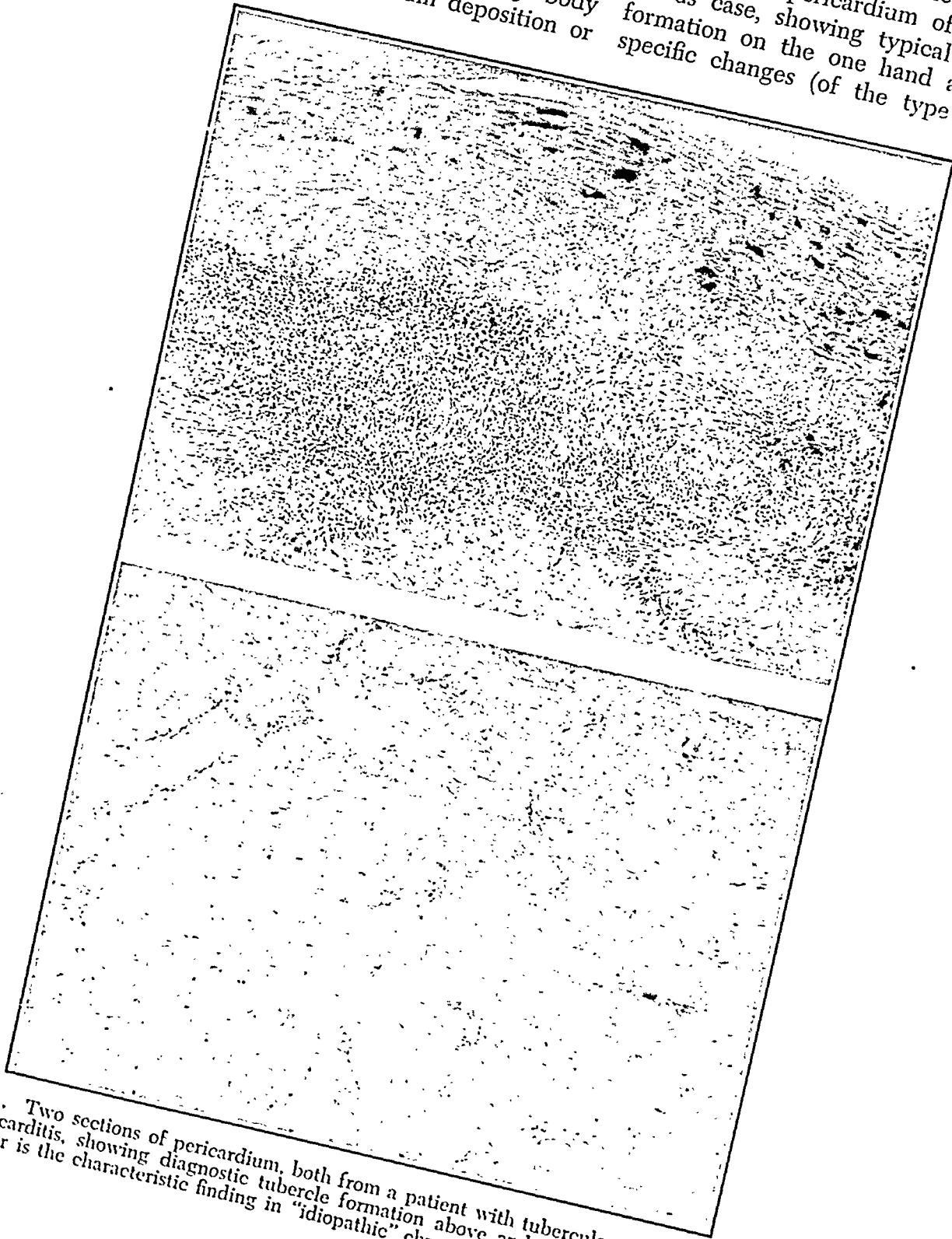


Fig. 1. Two sections of pericardium, both from a patient with tuberculous chronic constrictive pericarditis, showing diagnostic tubercle formation above and nonspecific fibrosis below. The latter is the characteristic finding in "idiopathic" chronic constrictive pericarditis cases.

encountered in "idiopathic" cases) on the other. It is important that in two cases healing tubercles were present in the operative specimens but no evidence of tuberculosis was found at post-mortem examination 2 and 3 years later.

It is not easy to distinguish between healed tuberculous and healed "non-tuberculous" constrictive pericarditis by history or by physical examination or by pathological study.

died at the age of 24 and was found at autopsy to have "chronic rheumatic endocarditis" with aortic stenosis. In no case, however, was there a history typical of rheumatic fever.

In 3 additional patients the past history contained highly suggestive, but not conclusive, evidence of a previous acute pericarditis. One of these patients had been acutely ill for 2 months with fever and pain in his precordial region 10 years prior to the onset of

Table 7. ETIOLOGICAL BACKGROUND

(53 Cases)

	Number of Cases	% of Total
Unknown	30	56.5
Tuberculosis	9	17.0
History of Acute Pericarditis	9	17.0
Previous acute pericarditis unaccompanied by other clinical abnormalities	4	
Previous acute pericarditis complicating:		
1) endocarditis with mitral murmurs, arthritis (with history of bilateral pneumonia and left pleural effusion 2½ years before); chronic rheumatic endocarditis and aortic stenosis at autopsy	1	
2) acute polyarticular rheumatism, endocarditis, myocarditis, bilateral hydrothorax	1	
Probable previous acute pericarditis with:		
1) 4-day illness at age of 16 months diagnosed as probable pericarditis	1	
2) episode of anterior chest pain, nausea, vomiting, diagnosed as coronary thrombosis	1	
3) 2-month febrile illness with precordial chest pain	1	
Miscellaneous	5	9.5
Pleurisy preceding onset of chronic symptoms	2	
Pneumonia preceding onset of chronic symptoms	1	
"Influenza" preceding onset of chronic symptoms	1	
History of "water on stomach and large liver" during a febrile illness of 2 months' duration 7 years prior to onset of chronic symptoms	1	
Total	53	100.0

A history of a *previous acute pericarditis* was obtained in 6 of the 53 cases. In this group there were 4 patients in whom an illness consistent with acute pericarditis alone, without major involvement of other structures, was described. In 3 of these, symptoms suggesting pericardial constriction followed soon after the initial acute involvement, but the patients did not come to us for treatment for 4, 2, and 1, years respectively. In the fourth case there was a 29 year period of good health after acute pericarditis followed by 2 years of dyspnea and ankle edema before we saw him. In the remaining 2 cases pericarditis was merely one complication of a more diffuse disease process, as indicated in Table 7. The latter group includes a patient who

his symptoms. Another had been hospitalized because of an illness with sharp pain across his anterior chest associated with nausea and vomiting, which was diagnosed as coronary thrombosis; in retrospect it appears that the probable correct diagnosis was acute pericarditis. The third patient was thought by her own physician to have had pericarditis at the age of 16 months, but a definite diagnosis was not made; shortly after this episode she developed the symptoms and signs of a chronic cardiac tamponade.

None of these patients was proved to have tuberculosis, pericardial or otherwise, and the causative factor or factors in their original pericarditis remains uncertain. In particular, we are not impressed by the evidence for

a rheumatic background to the group as a whole. Three of these 9 cases with a history of initial acute pericarditis are now living; pericardial calcification was found in 5 of them, and 3 showed auricular fibrillation.

Finally, mention should be made of 2 patients who gave a history of pleurisy ("without pericarditis") during the few months prior to the onset of their chronic symptoms and of an additional 2 patients whose initial acute illnesses were diagnosed as pneumonia and influenza respectively. There is, moreover, 1 patient who is said to have had smothering attacks, "water on her stomach and a large liver" during a febrile illness of 2 months' duration 7 years prior to the onset of her chronic symptoms. This could certainly have been acute pericarditis with effusion.

It is obvious that many of these patients had more than one type of serous membrane involved and that a polyserositis did in fact exist, idiopathic in origin. Such a designation is broadly inclusive and has a descriptive value; it does not, however, help to elucidate the nature of the disease process.

**6. Discussion.** That orthopnea is not one of the commoner symptoms in chronic constrictive pericarditis should not obscure the fact that shortness of breath itself is the most frequent complaint which these patients have. As we have seen, not only does it occur more often than any other symptom but also it is found most frequently as the initial complaint. Our investigations tend to rule out a concomitant hydrothorax, a high diaphragm from ascites, or the presence of auricular fibrillation or flutter as the significant factor, and point rather to constriction of the heart itself as being a most important element in its production. We have observed clinically that an increase of the intensity of the second pulmonic sound is often present as an

indication of an increased pressure in the pulmonary arterial system.

We have also noted at autopsy that the left ventricle (as well as the rest of the heart) undergoes constriction and that the pericardium overlying it is frequently calcified. It is logical to assume that in most patients with constrictive pericarditis it is the whole heart which is affected and not merely, or even predominantly, the chambers of the right side.

It is also important to stress the fact that the heart is not necessarily normal in size in constrictive pericarditis. Moderately large hearts occur in about one third of the cases, and occasionally even a very large heart is found. More valuable than determination of the heart size are Roentgenographic observations of the presence of pericardial calcification and the character of the cardiac pulsations. These studies, plus the electrocardiographic pattern previously described, are among the most helpful diagnostic tools, although they do not supplant a well taken history and a careful physical examination.

In many of our cases surgical removal of pericardium overlying the anterior surface of the heart, together with a lysis of lateral and apical adhesions, was adequate to relieve the mechanical embarrassment and allow essentially normal systolic contraction and diastolic filling. In a minority of the cases this procedure alone was not enough, and with this experience we anticipate that a more generous pericardiectomy will have to be performed at times in future patients if satisfactory results are to be achieved. The operation is not to be undertaken lightly, for these patients are often in a "poor risk" group and a single procedure may not be enough. As we have seen, the myocardium itself may be involved, in addition to disease of the pericardium, pleura, and liver. A

skilled surgeon is required, and close co-operation between him and the attending cardiologist is a prerequisite to success. It is probably wise to reserve operation for those patients whose symptoms significantly limit their activities and to treat by medical measures alone those who have only a minimal disability, especially if they are in the older age group.

Study of the etiological background of our cases provides an unsatisfactory answer to the questions: What is the cause of chronic constrictive pericarditis? Are all these patients suffering from the same disease? Are they all tuberculous in origin?

Harvey and Whitehill<sup>4</sup> state that of 17 patients with tuberculous pericarditis without effusion, 5 developed a clinical picture consistent with chronic constrictive pericarditis (all 5 died). More recently, Pickering<sup>6</sup> in London observed 16 cases of tuberculous pericarditis and has found that 14 of them progressed to the stage of pericardial constriction, 7 coming to surgery. Edwards<sup>2</sup> in Liverpool has also followed 8 patients with proved tuberculous involvement of the pericardium and has seen all of them develop the clinical picture of chronic constrictive pericarditis. The reported incidence of tuberculosis in patients suffering from chronic constrictive pericarditis itself varies: Blalock and Burwell<sup>1</sup> made a diagnosis of tuberculosis in 18 of their 28 cases; Pickering encountered 11 cases of chronic constrictive pericarditis (not drawn from the group of tuberculous pericarditis mentioned above) and believed that all but 1 were tuberculous in origin although actual proof was lacking.\* These and other reports, as well as our own data, emphasize that both tuberculous and chronic constrictive pericarditis predominate in

males, and that the onset of tuberculous pericarditis may be so insidious as to escape early detection. It is also clear that isolation of tubercle bacilli from pericardial, pleural, or peritoneal fluid is not readily accomplished.

Our small group of 9 proved tuberculous cases seems, as we have pointed out, to have an unusually short period of ill health, which to some extent distinguishes them from the rest of the cases in the series and which may explain the infrequency of cardiac arrhythmias and of pericardial calcification. We wonder why the other 44 patients with idiopathic constrictive pericarditis did not show signs of tuberculous involvement of other organs at some time; and we also wonder why pathological study of the pericardium was unrevealing in so many cases (although we have commented upon some possible reasons therefor). It may be postulated that these cases represent an old, burned-out tuberculous pericarditis analogous to an old tuberculous pleurisy, and hence that as in the latter condition microscopic study might not disclose typical tubercle formation. Evidence of an active inflammatory process was found at the time of operation on 6 patients, however, and in only 1 of these was the diagnosis of tuberculosis made by pathological examination of the section of pericardium removed. Although we believe that the theory of the tuberculous origin of essentially all cases of chronic constrictive pericarditis has much to recommend it, we are not able from our own studies as yet to state without reservation that other etiological factors may not also be important.

**Summary.** 1. In the period 1914 through May 1947, 53 patients with constrictive pericarditis have been seen

\* It should be mentioned that the differing incidence of proved tuberculous infection of the pericardium at the Massachusetts General Hospital and at other medical centers may be explained in part by differences in geographical location and type of patient seen.

at the Massachusetts General Hospital or in the private practice of one of us (P.D.W.). 2. Shortness of breath on effort was the commonest symptom and was followed in incidence by swelling of the ankles and legs, abdominal swelling, and abdominal discomfort. 3. The most common physical findings were, in order of their frequency, enlargement of the liver, prominence of the neck veins, ascites, peripheral edema, and signs of fluid and/or pleural thickening at the lung bases. 4. Cardiac enlargement (as determined by Roentgen-ray observations) was present in 29 cases (54.7%), and by fluoroscopy the cardiac pulsations were found to be diminished or absent in 32 of 40 patients so studied. Chest films also disclosed evidences of a unilateral or bilateral hydrothorax in 28 patients (52.8%). 5. Calcification of the pericardium was observed in 29 cases (54.7%). 6. Electrocardiograms were taken on 52 of the 53 patients and showed auricular flutter or fibrillation in 20 (38.5%), low voltage in 17 (32.6%), and abnormal T waves in the limb leads in 45 (86.5%). 7. Surgical exploration with pericardiolysis and parasternal pericardiectomy was undertaken on 42 of these patients. The results in 25 (60.9%) have been satisfactory. Six patients died as a result of the operative procedure itself, 5 died from complicating diseases, and 4 died from the effects of their underlying disease. The cause of death of 1 patient is not known. 8. Seven patients were too ill for surgery and died while receiving medical treatment. One patient died before the operative series began, 2 patients had such minimal symptoms that operation was felt to be unnecessary, and 1 patient has not been followed. 9. The etiology was entirely obscure in 30 cases (56.5%) despite the fact that sections of the pericardium were available for microscopic study in 46 of the 53 cases in the series. Tuberculous involvement of the pericardium was proved in 9 (17%). Healed (fibrous) scarring was the usual finding and this may or may not have resulted from tuberculous infection. A history of acute pericarditis of unknown origin was present in 6 cases (11.3%), and in 3 others (5.7%) the history was very suggestive of an episode of acute pericarditis in the past.

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# CHRONIC CONSTRICTIVE PERICARDITIS OVER THE LEFT HEART CHAMBERS AND ITS SURGICAL RELIEF

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A new development of importance in the diagnosis and treatment of chronic constrictive pericarditis in this country took place in the operating room in 1928 when a young woman, crippled by chronic constrictive pericarditis, was cured by surgery. This ushered in a new era which, during the past 20 years, has in large part fulfilled the hope originally raised. However, there have been difficulties particularly in the surgical relief of the minority of more obstinate cases. Surgical approach through the anterior wall of the chest was successful in the majority of those patients operated upon, but here and there were failures despite such operations even when they were repeated in the same cases.<sup>1,4,5,6</sup> During the past few years light has been thrown on at least one of the reasons for our occasional earlier failures and it is of this that we now write. We shall report 3 of our interesting and puzzling cases together with the methods used in deciding their future course.

homa on August 8, 1932, with the diagnosis of chronic constrictive pericarditis. In early childhood he had had chicken pox and measles; at 5 years of age a tonsillectomy was done. At 9 years he had "double pneumonia" and was in bed for 6 weeks. There was a complication of left pleural effusion and this was tapped. Cardiac enlargement and a systolic murmur were discovered then. At the age of 13 a routine examination showed some cardiac enlargement with a systolic murmur, pulsating veins in the neck and enlargement of the liver the edge of which was felt three finger-breadths below the costal border.

When 14 years old, during the winter of 1929-30, he noticed that his face was swollen and that he had some difficulty in getting on his waistcoat due to enlargement of the abdomen. Edema of the thighs was developing at that time and the liver was enlarged until its lower edge reached the umbilicus. He continued at school part-time for a year and then had to give up and was living a semi-invalid life when we saw him first at the age of 16. He had had very little dyspnea. Diuretics were used with temporary benefit. Two months before entrance to the Massachusetts General Hospital his abdomen had been tapped

Case Reports. Case 1. J.N., male aged 16, was referred to us from Okla-

and 8 liters of fluid removed. It should be stated that digitalis had been ineffective. There was nothing abnormal in the family history.

Physical examination showed a well developed and moderately well nourished young man lying comfortably in bed without dyspnea but with slight to moderate engorgement and pulsation in the jugular veins. The heart rhythm was absolutely irregular at a rate of 120 and the pulse was definitely paradoxical. The blood pressure was 110 mm. systolic and 95 diastolic. The heart showed moderate enlargement. The sounds were of fair quality. There was a loud blowing systolic murmur at the apex; there were no diastolic murmurs. A slight third sound was heard at the apex. The lungs were clear. The abdomen was uniformly prominent. There was slight edema over the anterior abdominal wall and over the shins. The heart shifted definitely on change in position of the thorax. The liver edge was not tender; it was easily felt extending across the abdomen half way between the umbilicus and the costal border. There was no Broadbent's sign, clubbing of the fingers, or pyrexia. The blood was normal. The urine showed the slightest possible trace of albumin with a rather high specific gravity due to restriction of fluid intake. Roentgen-ray examination showed definite enlargement of the heart shadow in all diameters, particularly in the region of the auricles. There was an increase in the supracardiac shadow thought to be due to venous congestion. Barium in the esophagus showed deviation to the right in the region of the left auricle. Pulsations were weak. The lung hilus shadows were increased and the pleurae were markedly thickened on both sides. The electrocardiogram showed auricular fibrillation at a ventricular rate of 80 with slight right axis deviation and inverted T waves in leads 2 and 3.

Pericardial resection was advised and on September 27th, 1932, this was done by Dr. Churchill,<sup>2,7</sup> utilizing the anterior approach. A very much thickened pericardium with some calcium deposit was found and dissected from the right ven-

tricle and the right auricle and in part from over the left border of the great vessels. A considerable portion of the diaphragmatic pericardium extending backward to the region of the inferior vena cava was removed. A considerable amount of calcified pericardium was left but the amount that was excised allowed the heart to herniate outward and greatly increased its diastolic filling. Microscopic examination of the pericardium which was removed showed hyaline degeneration of fibrous connective tissue with focal deposits of lime salts.

His postoperative condition was satisfactory but improvement was slow. In the course of the first week the anasarca seemed to be clearing somewhat and the cervical veins were less engorged. The venous pressure dropped from 28 cm. to 14 cm. After disappointingly slow progress and the use intravenously of mercurial diuretics on several occasions and abdominal paracenteses he returned to his home in Oklahoma where he remained 10 months. He returned in September 1933, showing considerable improvement but not adequately relieved. He had lost about 20 pounds in weight but still required an occasional abdominal paracentesis. The serum protein was 4.3 gm.% The liver function showed a 10 to 15% retention of the dye. His electrocardiogram showed auricular fibrillation with slightly low voltage and slight right axis deviation as before. Roentgen-ray examination showed some calcification which had not been definitely evident before. It was thought that further pericardial resection was indicated.

On November 16, 1933, Dr. Churchill<sup>2</sup> operated again with ease through the original scar which was excised. Calcified pericardium at the base of the great vessels was removed and the right ventricle was more completely freed. The left auricular appendage was dissected free. The pericardial tissue removed showed as before fibrosis with calcification. There was an uneventful recovery after this second operation but no further improvement, and on March 30, 1934, a Talma operation (omentopexy) was done because of the opinion that the liver con-

dition was now possibly responsible for the persistently recurring ascites. At the time of his operation a small bit of liver was removed and was found to show slight cardiac fibrosis. The liver capsule was not thickened (no frosting or Zuckergussleber). The boy's postoperative course was uneventful. It is doubtful that the omentopexy was followed by a real improvement in the patient's general condition.

The succeeding 18 to 24 months were devoted to dietary therapy and experimentation. The amount of fluid intake together with the salt intake was varied to observe if any changes in fluid retention might occur. It may be noted that after the institution of dietary restrictions the number of necessary abdominal paracenteses was reduced significantly. Prior to the dietary changes the patient was tapped at least once a week with a yield of between 6000 and 9000 cc. at each occasion. After a low salt and low fluid intake regime was observed for a sufficient length of time it was necessary to tap the abdominal cavity only once every 3 weeks with a yield well under the original 9000 cc. The relationship between salt and fluid intake and fluid retention in the serous cavities and peripheral tissues was apparent.

The patient's condition remained relatively satisfactory until December 19, 1940, at which time he suddenly became aware of a numbness of both legs below the hips. Both feet were very white, cold and dry. Femoral pulsations were lacking. Cardiac examination revealed no definite change from the previous record; auricular fibrillation was still present. A right and left common iliac embolectomy together with a right femoral embolectomy were performed immediately with a return of the right femoral pulsations. Large emboli were removed from all three arteries. Postoperatively the use of anticoagulants, Pavaex boots and a lumbar sympathetic block seemed of no benefit. The patient's condition gradually became worse; both legs became more and more discolored and he complained of tingling in the left leg and no sensation in the right. On December 22,

1940, while attempting to turn over in bed he became extremely short of breath, gasped and expired.

"Necropsy: The body is that of a well developed well nourished 25 year old man measuring 171 cm. in length and weighing 145 pounds. There is an old semicircular well healed precordial incision measuring 18.5 cm. in length. The anterior portion of the left fourth, fifth and sixth ribs as well as a portion of the sternum are absent. There is also an old well healed right upper quadrant paramedian incision measuring 4 cm. Pitting edema extends up both legs to just above the knees. The scrotum is enormously enlarged, measuring 20 cm. in diameter, and is soft; a fluid wave is easily demonstrated. The muscles are red brown and negative.

"*Peritoneal cavity* contains about 1000 cc. of this yellowish fluid. The peritoneum itself is markedly thickened, tough and fibrous. It measures in some places 5 mm. in thickness. *Appendix, esophagus and stomach*: essentially negative. *Intestines* show moderate distention. *Retroperitoneal glands* negative. *Margin of the liver*: the liver edge is 2 cm. below the costal margin in the right mid-clavicular line and 4 cm. below the zyphoid. *Diaphragm*: right side at fifth interspace; left at sixth rib.

"*Pleural cavities*: the right pleural cavity contains about 2000 cc. of thin straw colored fluid. Extending between the right lower lobe and diaphragm in the medial and posterior part are numerous thick fibrous smooth adhesive bands resembling enlarged chordae tendineae and measuring up to 2 to 3 mm. in diameter. The left pleural cavity contains 500 cc. of similar fluid. The left upper and lower lobes are densely adherent to the parietal pleurae and separate with only the greatest difficulty. *Trachea, bronchi and bronchial glands*: negative. *Lungs*: the right lower lobe is moderately firm throughout and on section numerous hemorrhagic foci 3 to 6 mm. in diameter are found. Near the costophrenic angle the hemorrhagic areas are confluent and suggest bronchopneumonia rather than infarction. Similar but

less extensive foci are seen in the left lower lobe. The openings of the pulmonary veins are free from thrombi.

*"Mediastinum and pericardium:* on removing the chest plate the tissue underlying the previously mentioned scarred area is found to be tough and fibrotic. An area measuring approximately 6 by 5 cm. of the lower anterior portion of the pericardium has been surgically removed. In its place is a moderate amount of fibrous scar tissue which is adherent to the under surface of the operative wound, but which separates easily with blunt dissection. The remaining portion of the anterior parietal pericardium is for the most part fibrous and adherent to the visceral layer. The upper two-thirds of the left antero-lateral portion of the pericardial cavity is completely inseparable and obliterated by irregular confluent masses of calcium, extending cephalad to involve the base of the aortic valve and forming a large plaque measuring 9 by 6 cm. in extent. The outer surface of this plaque is covered by fibrous tissue which in turn is adherent to the mediastinal parietal pleura of the left lung. This plaque extends somewhat posteriorly to impinge by external pressure upon the lumen of the mitral valve. There is no calcification of the pericardium in the region of the apex of the left ventricle. There is a similar but somewhat smaller zone of pericardial calcification involving the antero-lateral aspect of the right ventricle over an area measuring 9 by 4 cm. On this side however, the calcification extends almost to the apex of the right ventricle but not as high up as the level of the pulmonary artery. Posteriorly the pericardium is free of calcification.

*"Heart:* The heart is not dissected free from the pericardium and lungs but opened in situ. The myocardium is red brown. The right ventricular wall thickness measures 3 to 4 mm.; the left, 13 to 15. The left auricle is enlarged; its cavity measures 8 by 6 by 4 cm. The remaining cavities and columnae carneae are essentially negative. The lateral aspect of the mitral valve is pressed on externally by the calcified

pericardium resulting in definite mitral stenosis. The aortic valve is moderately thickened and shows slight but definite interadherence of the cusps at their commissures. The other valves are essentially negative. The coronary arteries are negative.

*"Aorta:* The thoracic and abdominal aorta is normal. The right common iliac artery and its branches show no evidence of obstruction due to secondary thrombosis or emboli. The arteriotomy wound is plainly visible and well healed. Dissection of the common femoral on the right shows an embolus at its bifurcation which obstructs both the superficial and the profunda femoral vessels. There is a secondary clot extending into the superficial femoral for an indeterminate distance. The profunda femoral on the other hand is plugged with a secondary thrombus for only a short distance. On the left there is an extensive thrombosis in the external iliac artery with thrombosis at the site of the arteriotomy wound of the common iliac artery. Thrombosis also extends into the left hypogastric artery. This thrombosis extends down to the origin of the deep epigastric artery where it stops. There seem to be areas of old thrombus formation in this area of blood clot suggesting that all the emboli had not been removed at the time of operation. This also would be borne out by the fact that following the removal of the embolus of the left common iliac artery there was no back bleeding from the external iliac artery. Dissection of the left common femoral artery shows another embolus at the bifurcation with a secondary thrombus formation extending into both the deep and superficial femoral arteries.

*"Pulmonary artery:* normal.

*"Vena cava:* The inferior vena cava is greatly dilated, measures 2.6 cm. in diameter, and at its diaphragmatic opening easily admits two fingers throughout the entire extent.

*"Diaphragm:* Is markedly thickened and measures up to 0.8 cm. in thickness. The inferior surface is coated with icing and also shows a trabeculated aspect near the crux. This is most marked on both sides of the round ligament.

*Liver:* Weighs 1400 gm. Most of the anterior and diaphragmic surfaces of the liver are covered with icing. Its entire surface is irregular and nodular, the nodules measuring up to 1.3 cm. in diameter. On section it is extremely tough and fibrous, being light red brown in color. Bile ducts: Normal. *Pancreas:* Is encased in tough fibrous peritoneum. *Spleen:* Is moderately fibrous and is covered in spots by grayish white tough icing. It is estimated to weigh 350 gm.

*Adrenals:* Normal. *Kidneys:* Weight 275 gm. In the lower pole of the right kidney is a mottled red and white area measuring about 9 cm. in diameter. On section this area is soft and extends well down through the cortex. The cortex measures 7 mm. The pelves are normal. Ureters, bladder, and prostate: Normal. *Scrotum:* There are large bilateral indirect inguinal hernias extending far down into the scrotum and containing thin straw colored fluid. *Bone marrow:* red. *Brain:* essentially normal.

**Microscopic Examination:** *Heart:* A section taken through the heart and pericardium shows the very markedly thickened pericardium adherent to the myocardium, there being only a thin line of areolar tissue separating them. This plane of cleavage is penetrated at frequent intervals by fibrous strands which extend down into the myocardium. The myocardium itself shows a slight increase in fibrous tissue which separates the muscle bundles.

*Lungs:* Lung tissue through the right lower lobe shows extensive pleural fibrosis beneath which are focal areas of atelectasis. The hemorrhagic foci noted grossly vary in structure. Some show merely alveoli filled with fluid, others with red blood cells and a few with occasional polymorphonuclear leukocytes. Although those containing the red blood cells are slightly suggestive of infarction the presence of intact alveolar walls and their irregular shape are more in keeping with focal hemorrhage.

*Liver:* The capsule is tremendously thickened and fibrotic and in one area a liver lobe has been entirely surrounded. The remainder of the liver shows an increase in the interlobar fibrous tissue.

*Pancreas:* Dense fibrous tissue surround the pancreas which it itself normal.

*Spleen:* Splenic capsule is markedly thickened and fibrotic.

*Kidneys:* A section through the area of the lower pole of the right kidney noted in the gross shows early necrosis of the tissue. There is infiltration of the tissue by polymorphonuclear leukocytes and considerable cellular debris. In a few places the normal architecture is partially destroyed, leaving mere shadows of tubules and glomeruli. Other sections of the kidney show slight congestion.

*Necropsy Diagnosis:* Adhesive constrictive pericarditis with calcification; embolism, left common iliacs; anasarca; peritonitis, chronic fibrous, generalized; pulmonary edema; renal infarct, right; operative wounds; left lower paramedian; right inguinal recent; right upper quadrant paramedian left; pericardiolysis; peripheral edema; ascites; perihepatitis and perisplenitis, chronic; endocarditis, chronic rheumatic with stenosis, aortic and ? mitral; dilatation of the venae cavae; hydrothorax bilateral; pleuritis, chronic fibrous, bilateral; pleuropericarditis, chronic left; cirrhosis of the liver, cardiac."

**Comment:** This was one of our earlier experiences with the vicissitudes of the treatment of chronic constrictive pericarditis. Although the patient was somewhat helped by surgery the result was still quite unsatisfactory. As seen in the report of the necropsy examination the amount of constricting calcified pericardium still present could readily account for the presenting symptoms and signs by virtue of the compression of the left heart chambers. The existence of the prominent pulmonary second sound was evidence against the presence of an atonic right ventricle. Even at that early date the importance of the salt intake in relation to the degree of fluid accumulation was shown by the results obtained with variations in the diet. A few of the presenting problems might have been answered if at that time cardiac catheterization had been avail-

able as a diagnostic procedure, as will be demonstrated in the following two cases.

Case 2. R.P., male, aged 21 years, was referred to us from western Pennsylvania on September 15, 1944, with the diagnosis of chronic adhesive pericarditis. His early childhood was uneventful except for scarlet fever at the age of 7 years. We could obtain no familial history of tuberculosis. In March 1943, he was rejected for duty in the armed services because of the findings by routine Roentgen-ray examination of the chest consistent with the diagnosis of chronic calcific pericarditis. Although asymptomatic he consulted his local family physician who found his electrocardiogram compatible with the diagnosis of constrictive pericarditis and referred him to the Massachusetts General Hospital for treatment.

Physical examination revealed a well developed and well nourished young man in no distress. His blood pressure was 102 mm. mercury systolic and 80 diastolic. His pulse was regular at a rate of 80 and was paradoxical. The neck veins were not pulsating. Both lung fields were clear. The heart was not enlarged to percussion. The sounds were of good quality. The pulmonary second sound was greater in intensity than the aortic second sound. There were no murmurs and no third heart sound could be heard. The abdomen was not distended nor was liver or spleen enlarged. There was no evidence of peripheral edema.

Venous pressure on admission measured 117 mm. water (Burwell end point; normal upper limit). The total serum protein was 7.4 gm. per 100 gm. Both blood and urine were normal. The electrocardiogram by virtue of the inverted T waves in all leads was consistent with the diagnosis of constrictive pericarditis. Roentgen-ray examination of the chest revealed a calcified pericardium and evidences of old pleurisy at the left base with a very small amount of fluid in the right pleural cavity.

On October 6, 1944, Dr. Richard Sweet performed a pericardiectomy using the anterior approach. The entire anterior portion of the pericardium including a

calcified band 1½ inches in width opposite the auriculoventricular groove was removed. This band also extended around and behind the apex. The patient's post-operative course was uneventful. On the day of his discharge (October 28, 1944) his venous pressure was, however, slightly elevated as shown by the venous pulsations in the neck extending 2 to 3 centimeters above the right clavicle. Fluoroscopy revealed relatively little change in the heart size. The cardiac pulsations remained poor. Both lung fields were hazy. In spite of these findings it was felt that the progress of the development of congestion might have been halted and that with further convalescence a more complete recovery might ensue.

During 1945 the patient's condition was fairly satisfactory. His venous pressure, however, remained elevated. Small rations of digitalis were prescribed to increase the tone of the right ventricle. Physical examination remained essentially unchanged. The electrocardiogram showed some improvement in the height of the T waves which were, however, still abnormal. The patient did light secretarial work throughout the year with no difficulty. We believed that there was still some pericardial constriction and calcification together with right ventricular atony.

On June 5, 1946, the young man again was admitted to the Massachusetts General Hospital. His was a history of progressive increase over a 2 to 3 month period of the size of his abdomen, shortness of breath, and increase in weight. He had been admitted to his local hospital for the treatment of an episode of acute congestion apparently secondary to tachycardia due to a change of rhythm from normal to that of auricular fibrillation. The physical findings of note included an increase in the venous pulsations in the neck (venous pressure of 265 mm. of water), rales at both lung bases with a question of an increase in the amount of fluid at the right base, cardiac enlargement with sounds of fair quality but with the pulmonary second sound of greater intensity than the aortic second sound, and a slightly enlarged tender liver.

Peripheral edema was also noted at times. His blood pressure was 108 mm. mercury systolic and 84 mm. diastolic and the heart rate was grossly irregular at 82. The Roentgen-ray film of the chest showed an increase in the heart size together with extensive calcification of the pericardium. The electrocardiogram confirmed the presence of auricular fibrillation and showed no improvement in the T waves; there was a change in axis deviation toward the right. Blood and urine examinations were within normal limits. The total serum protein measured 7 gm. per 100 gm.

On June 20, 1946, Dr. Richard Sweet performed the second pericardiectomy, the site of the original incision being used again. On this occasion a constricting band of calcified pericardium was removed from the area of the right auriculoventricular groove. The right ventricle was seen to fill more rapidly thereafter and the blood pressure rose. Once again the patient's postoperative course was uneventful. Although a little short of breath on discharge on July 13, 1946, he seemed much improved clinically. The venous pressure then measured 200 mm. water.

While at home he adhered strictly to a medical regime consisting of a low salt diet, digitalis, ammonium chloride and intravenous mercupurin as needed. Within a month of his return home, however, his original symptoms recurred.

On December 10, 1946, he returned to the Massachusetts General Hospital. He was obviously much worse. Shortness of breath was noted even while he was lying in a semi-erect position in bed. His cough was persistent. The neck veins were very prominent and pulsating, with venous pressure of 300 mm. water. There was evidence of fluid at both lung bases. Cardiac enlargement was apparent and the heart sounds were mediocre in quality. A paradoxical pulse was present with rhythm irregular at 82. The blood pressure was 108 systolic and 76 diastolic. There was a third sound at the apex without murmurs. The pulmonary second sound was of greater intensity than the aortic second sound. The liver edge was

felt 7.5 cm. below the costal margin and was slightly painful to palpation. There was slight to moderate edema of the ankles bilaterally.

Future management of this case demanded that we determine which of the following factors was most important in causing the persistence of the congestion and that we govern any further surgery with this in mind:

1. Obstruction to the entrance of blood into the heart through mediastinal constriction of inferior and superior venae cavae and of the right auricle.

2. Failure of an atonic right ventricle which had been very probably involved in a subepicardial myocarditis in the development of the chronic constrictive pericarditis.

3. Constriction of the left heart chambers or of the left auriculoventricular groove acting like mitral stenosis to cause chronic right heart failure.

We decided to use cardiac catheterization as a diagnostic aid in determining the pulmonary arterial pressure. Dr. Lewis Dexter<sup>3</sup> kindly made this test for us and in demonstrating a three-fold increase above the normal of the blood pressure in the pulmonary circulation confirmed our clinical impression of constriction of the left heart chambers as indicated by accentuation of the pulmonary second sound and by the shift in the electrocardiographic axis towards the right. The pulmonary arterial pressure was found to be 72 mm. mercury; the normal averages 25 mm.

With this fact as a guide the surgeon could thus focus his attempts at decortication of the left auricle and left ventricle primarily, creating an adequate exposure by using the transthoracic or thoracotomy approach. On January 17, 1947, after the optimum preoperative condition was reached by medical measures a third pericardiectomy was performed by Dr. Richard Sweet. The left transthoracic approach was utilized. The pericardium was released from the apex, and the area behind the left auricle and left ventricle was released from the diaphragm and as far around in back as the inferior pulmonary vein.

Superiorly it was freed over the auriculoventricular groove and the auricular appendix of the auricle. A very wide liberation of the left ventricle and the left auriculoventricular septal groove was accomplished. Dr. R. H. Sweet's operative note was as follows:

"A long oblique incision was made starting in front close to the previous pericardiolysis incision, extending laterally under the breast and up beneath the pectoral fold as far as the midaxillary line. This incision was enlarged through the 6th interspace and on inserting a rib-spreader, after freeing the adhesions of the lung, an excellent exposure was obtained. The lung was densely adherent to the parietal pleura both beneath the ribs and along the mediastinal surface. The mediastinal adhesions were separated and the lung was retracted posteriorly and laterally. This gave an excellent exposure to the left posterior aspect of the pericardium. The phrenic nerve was identified and held aside with a retractor. The previously denuded section of heart appeared to be functioning well. This included the right ventricle and a very small portion of the left. The apex had been freed previously, but there had been considerable re-formation of constricting fibrous tissue in this region. This was freed and the remainder of the pericardium, which enveloped and held in a constricting vise the left ventricle, was released with moderate difficulty. It was adherent almost everywhere, however, by very dense adhesions, in some of which were actually plaques of very thick calcium requiring cutting with heavy scissors, but it was possible by freeing them to release the left ventricle completely all the way around behind. The pericardium in this region was removed from the diaphragm and as far around in back as the inferior pulmonary vein. Superiorly it was freed over the auriculoventricular groove, and the auricular appendix of the auricle which was held down in a vise of calcium was finally freed and was seen to retract upwards. A rather large segment of pericardium was removed from the auricular portion as well as the ventri-

cular portion. It was felt at the completion of the operation that a very wide liberation of the left ventricle and left auriculoventricular septal groove had been accomplished. The patient stood the operation well and the color of his blood was normal at its completion although in the beginning he was very cyanotic until the heart had been freed. The lung expanded well. A catheter was left in the space between the heart and the lung in order to provide for evacuation of serum and possibly any air which might result from an undiscovered leak from the lung itself. This was brought out through the center of the incision and is to be removed in 24 hours. The wound was closed in layers by means of interrupted silk sutures with several pericostal sutures of catgut in the intercostal portion of the incision."

The patient's postoperative course was a stormy one through which he was helped by the use of digitalis, quinidine, ammonium chloride, and mercurial diuretics. Throughout his hospital stay the predominant cardiac rhythm was one of auricular flutter. Over a period of 4 to 6 weeks he began to improve as noted by a decrease in respiratory difficulty, a decrease in the size of the liver, and in the amount of peripheral edema, and a decrease in the venous pressure which by the end of February, 1947, had receded from 265 to 190 mm. of water.

Following his discharge from the hospital on March 4, 1947, he remained at home and gradually increased his activities in direct proportion to his general clinical improvement. By the fall of 1947, he was able to walk a long distance without any respiratory embarrassment, to dance, and to increase his minor activities to the maximum. He was easily maintained on digitalis alone and the proof of this reported improvement is mirrored in the fact that his venous pressure in December, 1947, had decreased to 167 mm. of water. Hope for the future seemed bright.

On August 27, 1948, his physician, Dr. M. H. McCaffrey of Pittsburgh, wrote of his excellent health with no evidence whatsoever of congestion of liver, extremi-



ties, neck veins, or lungs. There was still present auricular fibrillation at a well controlled heart rate of 72. He was fully active and able to swim and dance without symptoms.

**Comment:** Cardiac catheterization has to the present time found much of its clinical usefulness in the diagnosis of congenital malformations, but the adaptability of this procedure as an aid in the localization of the site of constriction has been illustrated in this case and can best be presented graphically: See Fig. 1.) If at Site No. 1 (superior vena cava) the pressure is found to be increased above normal one

may suspect constriction around the point of entrance of the great vessels or of the right auricle or right ventricle. This condition would of course prevail in those cases in which there is no important increase in the size of the heart. A pressure increase or even a normal value with a normal pulse pressure at Site No. 2 (right ventricle) would tend to rule out both right ventricular atonia and constriction of the right ventricle, which gives a low pulse pressure in the right ventricle. This would be substantiated by the presence of an increased pulmonary second sound. An increase in the

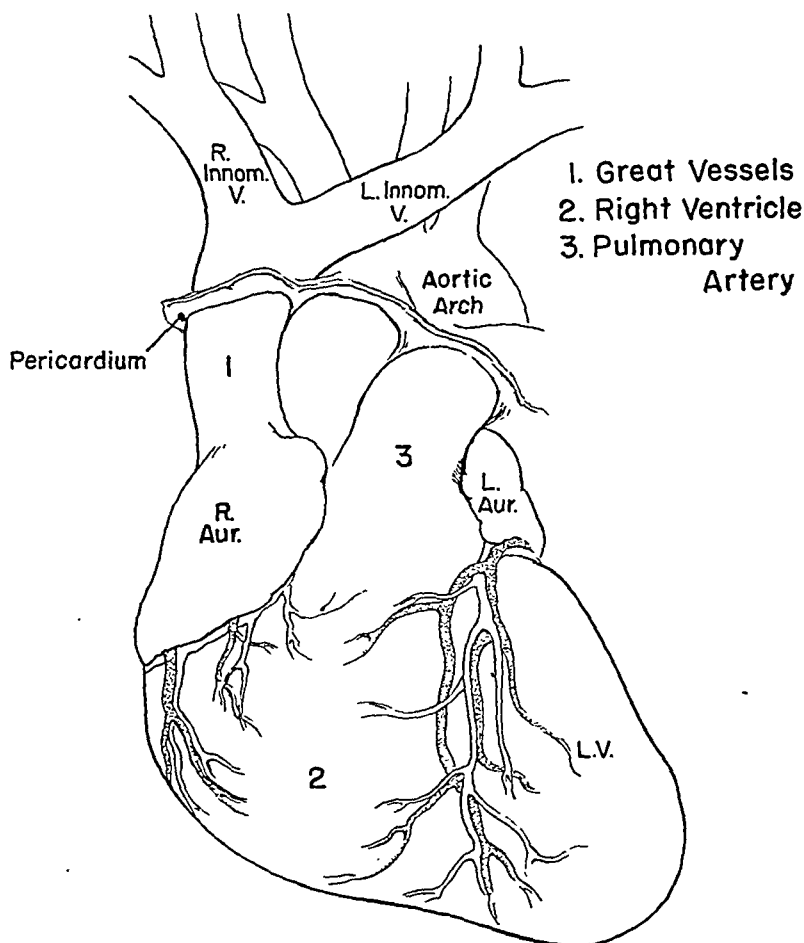


Fig. 1. Diagram of heart to illustrate the positions from which blood was taken by catheter for determination of oxygen content in Case 2.

pressure at Site No. 3 (pulmonary artery) means that the constriction is beyond the right ventricle, presumably in the left heart chambers. Cardiac catheterization is not a formidable procedure and may be of immeasurable aid as a preoperative diagnostic procedure in cases of chronic constrictive pericarditis.

Case 3. R.J., male, aged 20 years, was admitted to the Massachusetts General Hospital on November 17, 1947, because of the onset of dyspnea, syncopal attacks and swelling of the abdomen over a 10 to 12 months period. The patient was rejected for duty in the armed services because of the finding of an enlarged heart by routine Roentgen-ray examination. Because of the continuation of his symptomatology in spite of medical therapy he was referred to this hospital. His family and past history were noncontributory. There was no history of tuberculosis or of any acute infection.

On admission this well developed and well nourished young man was in no acute distress. His neck veins were full. The lung fields were clear. The heart was enlarged to percussion and totally irregular in rhythm at a rate of 72. The heart sounds were of good quality. The blood pressure was 110 systolic, 70 diastolic. There was a double second sound at the base and a third heart sound at the apex, without murmurs. There was no gallop. Of note were the paradoxical pulse, the accentuated pulmonary second sound, and the retraction of the second and third interspaces on the left during systole (Broadbent's sign). The abdomen was prominent and revealed a fluid wave. The liver was enlarged, with edge 3 cm. below the costal margin. The spleen could not be felt nor was there any peripheral edema. The Roentgen-ray film of the heart showed it to be enlarged with considerable prominence of the left auricle and of both ventricles. There were plaques of calcium surrounding the heart incompletely in a circular manner. The electrocardiogram showed auricular flutter-fibrillation with ventricular rate of 90, normal axis, flat T waves in Lead 1,

diphase T waves in Lead CF5, with inversion of all the remaining T waves. This was in keeping with the diagnosis of chronic constrictive pericarditis. The urine and blood were within normal limits. The total protein was 7.35 gm. per 100 gm. with albumin globulin ratio of 1.6. The venous pressure was 270 mm. water. Because of our previous experience of the diagnostic value of cardiac catheterization our associate Dr. Gordon Myers carried out the procedure and determined the pulmonary arterial pressure. This proved to be twice its normal value and thus, as in Case 2, indicated the need of decorticating the left ventricle first. In withdrawing the cardiac catheter and taking continuous readings there was no evidence of atonia of the right ventricle or constriction around the great veins.

On December 5, 1947, after the patient had been prepared preoperatively with digitalis and quinidine Dr. Edward Churchill performed a pericardiectomy by the left transthoracic approach. The incision extended from the midline anteriorly to the midaxillary line over the fifth rib on the left. On exposure the anterior portion of the pericardium seemed relatively free of calcium. A large pericardial calcareous plaque, measuring 3 by 2 cm., over the left auricular appendage and upper portion of the left ventricle was removed. Then the pericardium was removed almost entirely from the left side of the heart posteriorly to the midline. Finally the auriculoventricular groove on the left was exposed and the pericardium was almost entirely removed therefrom. Several centimeters of the left side of the diaphragmatic portion of the pericardium were next removed together with a 2 cm. strip of pericardium anteriorly.

The postoperative course was eventful, in that spontaneous diuresis occurred, the patient's weight falling 12 to 14 pounds during the first 11 days after operation. Venous pressure at the end of this time was 185 mm. water. The ventricular rate in the auricular flutter-fibrillation seemed well under digitalis control. Of note was a loud third heart sound at the apex. On December 13, 1947, the patient's satisfactory condition permitted

discharge to his home. There was no remarkable change postoperatively in either the Roentgen-ray shadow of his chest or in the electrocardiogram. The patient was seen 13 days after his discharge and was in the best of spirits and health. He drove his car more than 100 miles just to keep this appointment 3 weeks after his operation and was none the worse for it.

When last examined in the Outpatient Department on July 21, 1948, he was in excellent health, working during the summer and planning to resume school in the autumn. There was no evidence of congestion of neck veins, liver, or lungs. The heart rhythm was irregular at a rate of 80 on daily digitalis therapy.

**Comment:** This is another case in which the success of our present-day surgery was directly dependent upon the careful preoperative studies, including cardiac catheterization.

**Summary.** We have herewith reported 3 cases, all male, aged 16, 21, and 20 years respectively, who suffered from chronic constrictive pericarditis involving preponderantly the left heart chambers and who required decortication thereof for relief. The first patient died from the complication of

peripheral arterial embolism after two unsuccessful pericardial resections carried out by anterior approach and an omentopexy. The other 2 patients have been greatly benefited, in fact probably cured, as a result of a trans-thoracic approach allowing free exposure of the side and the back of the heart. The pericardium was removed from the left auricle and left ventricle in these cases. In the first patient, two unsuccessful operations had previously been carried out through the usual anterior approach.

In these 3 patients clinical evidence suggested the correct diagnosis and consisted of accentuation of the pulmonary second sound, cardiac enlargement involving the right ventricle, and a shift of the electrocardiographic axis deviation to the right, with a persistence of chronic congestion. A measurement of the pulmonary blood pressure by cardiac catheterization has been an important test of the left heart chambers in the last 2 cases, confirming by its marked elevation the constriction of the left heart chambers which has acted like mitral stenosis on the pulmonary circulation and right heart.

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## CHYLURIA: A REPORT OF TEN CASES

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CHYLURIA is a rare but definite entity which has been recognized since Moellenbroccius,<sup>9</sup> in 1670, first designated the condition as chyle in the urine. The writings of Hippocrates, Galen and Theophilus mention fatty and oily urine,<sup>14</sup> and various writers of the Middle Ages described an "excretion of milk," the significance of which was not understood. Wucherer, in 1866, was the first to recognize the relationship between filariasis and chyluria when he demonstrated the presence of microfilaria in the blood and urine of a patient who had chyluria<sup>5</sup>. The physiologic and pathologic studies of Manson, Mackenzie and Block<sup>13</sup> further proved this relationship, and today, chyluria is a well-recognized and fairly common complication of filariasis. Most authors make a sharp distinction between parasitic chyluria, secondary to filariasis or rarely to other parasitic diseases, and nonparasitic chyluria, for the most part of unknown origin.

Carter, in 1862, first suggested the hypothesis of lymphatic obstruction with subsequent abnormal communication between the lymphatic system and the urinary tract (Kutzmann<sup>9</sup>). This undoubtedly occurs in filariasis, in which there is obstruction by a filarial granuloma somewhere between the draining lymphatic ducts of the small intestine and the cephalic end of the thoracic duct. As a result, there is a

backflow of chyle into the pelvic lymphatics, from there into a collateral lymphatic system of the abdominal wall, thence into the thoracic duct somewhere above the level of the diaphragm. It is postulated that an incompetency of this collateral system is necessary in order for chyluria to occur. If such an inadequacy exists, back pressure develops in the lymph vessels of the lumbar channels to the kidney, causing rupture of the vessels and subsequent spilling of chyle into the urinary tract. Pathologic studies by Mackenzie and Manson substantiated this hypothesis for the most part (see R. P. Strong)<sup>16</sup>. However, patologic support for this hypothesis when it is applied to nonparasitic chyluria is questionable or lacking. This is in part due to technical difficulty in demonstrating lymph channels in portmortem studies. A secretory hypothesis proposes that the chyle passes directly through the renal epithelium into the urine. This hypothesis is entirely unsupported by objective data. The mechanical hypothesis, then, remains the best explanation to date. Obstruction of the thoracic duct by other lesions, with secondary chyluria, undoubtedly can occur. Posterior thoracic lesions, perirenal abscess, pregnancy, syphilis, tuberculosis and other conditions have all been blamed for the presence of chyluria<sup>15</sup>. However, in few of the cases reported has there

been pathologic proof for the etiologic role of the suspected lesion.

In considering the etiology of chyluria, filariasis should always be kept in mind, even when one is dealing with patients in a temperate climate. A knowledge of the patient's travels is important. The southeastern part of the United States is a filarial endemic region. We suggest also that sporadic filariasis may occur, just as sporadic malaria may occur, in any region where mosquitoes are found. The absence of microfilariae in the blood and urine does not exclude a diagnosis of a previous filarial infection nor of pathologic conditions of filarial origin. A high percentage of persons who have a history of previous filarial infection do not show microfilariae in the blood or urine.

The location of the fistulous opening between the lymphatics and the urinary tract may be found anywhere from the kidney to the urethra. In the large majority of instances it is in the pelvis of the kidney.

The incidence of chyluria is, as expected, high in endemic filarial regions. Ray and Rao<sup>13</sup> have reported 254 cases from India. It is of interest to note, however, that whereas filariasis flourishes in some parts of the South Pacific, chyluria in those regions is negligible. More than 100 cases of so-called nonparasitic chyluria in Europe were reported in the literature prior to 1925, according to Kutzmann<sup>9</sup>. Yamauchi<sup>22</sup>, in 1945, reviewed data on 45 patients seen by him in Hawaii. In direct contrast, a careful search of the literature from the United States reveals that only 26 cases (including 5 of the 10 reported in this paper) have been recorded since 1916<sup>2-4,6-12,14,17-21</sup>. Twenty of these were designated as being cases of so-called nonparasitic chyluria.

Clinically, the symptoms of chyluria

are few. The patient usually complains of passing milky, cloudy or white urine, occasionally containing clots. These clots are coagulated chyle and, if formed in the pelvis of the kidney, the ureter or the bladder, they may cause dysuria. Hematuria is comparatively rare. The milky appearance of the urine is due to a colloidal suspension of fat particles, in distinction to lipuria, in which the fat is in the form of globules visible to the naked eye and stainable with Sudan III. Characteristically, the urine does not clear on centrifugation. Pyelographic studies occasionally show the presence of a pyelolymphatic type of backflow<sup>1</sup>. This is not a constant finding of chyluria, and backflow has been reported to be present in the absence of chyluria.

The ages of our patients when they were examined varied from 30 to 64 years. The average age was 47.4 years. The age at the onset of symptoms varied from 19 to 58 years. The average age at onset was 38.3 years. There were four men and six women. Two of our patients lived in Puerto Rico, 1 in British Guiana, 2 in Illinois, 1 in New York, 1 in Arkansas, 2 in Minnesota and 1 in Canada. At least 7 of these 10 either lived in a place where they may have contracted filariasis or had visited places where they could have contracted this infection. Our patients' weights were all normal or greater than normal with the exception of one patient who was slightly underweight. None of our patients had serious symptoms due to chyluria nor was their general health impaired by the chyluria. All passed milky urine; 2 passed chylous clots. The blood of 7 patients and the urine of 5 patients were examined for the presence of microfilariae and in each instance none was found.

Numerous types of therapy have

been employed in the treatment of chyluria, one of the commonest being the instillation of sclerosing solutions into the renal pelvis in an attempt to close the lymphatic fistula. Evaluation of such treatment is difficult, inasmuch as chyluria is characteristically intermittent and recurrent over many years. The use of sclerosing solutions is rarely, if ever, indicated, because the affliction seldom causes the patient any significant distress, and it has been repeatedly proved that the loss of fat and protein in the urine is negligible so far as the nutritional status of the patient is concerned. Arsenical preparations have been employed rather frequently in the tropical countries; but again, as with any type of treatment of chyluria, the results are difficult to evaluate, and in this case, the rationale for such therapy is not understood. Rarely do these patients require any form of specific

therapy. It seems to us that there are two conditions which, if present, may need treatment: (1) undernourishment, due to loss of fat through the urinary tract; (2) the presence of fat in the urine in such large quantities that it will precipitate or solidify and form clots prior to excretion. These clots may cause considerable pain and dysuria.

The malnutrition can be controlled by increasing the patient's caloric intake. We believe that one could maintain normal weight and health even though he lost almost all of his fat intake through the urinary tract. This loss could be made up by increasing his carbohydrate and protein intake. The excessive amount of fat in the urine that produces clots can, we believe, be controlled in most instances by reduction of the fat intake, as was shown in case 10, in which, on his

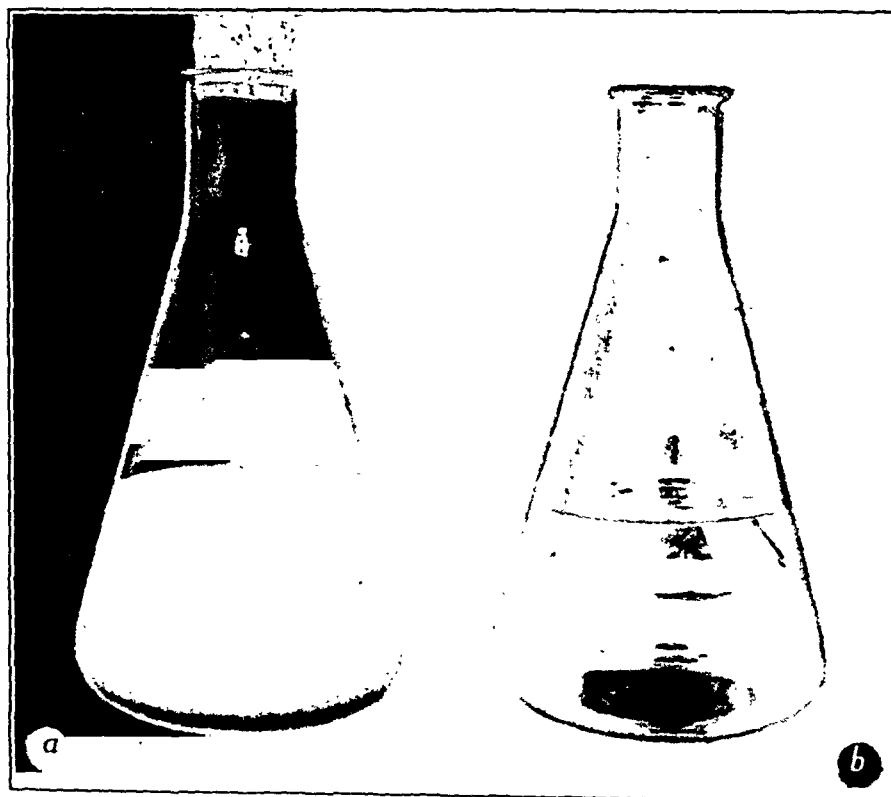


Fig. 1a.—A specimen of urine from Case 10. The specimen contained 988 mg. of fat per 100 cc. of urine. b. A specimen of normal urine.

usual diet, the patient had 402 mg. of fat per 100 c.c. of urine. On a high fat diet the urine contained 988 mg. per 100 c.c. (Fig. 1) and on a low fat diet it contained only 100 mg. of fat per 100 c.c.

**Report of Cases. Case 1.** A 47 year old white man was seen at the Mayo Clinic in July, 1932. He complained chiefly of postprandial bloating and belching. Other symptoms of which he complained included insomnia, nervousness and milky urine, the last of which had been present since the age of 21 years. His residence was Arkansas and there was no mention of areas visited by travel except that he had never been outside of the United States. At onset, the milky urine was present daily, particularly in the morning, 2 or 3 hours after breakfast. In more recent years, milky urine had been noted to be present only about once yearly. Physical examination revealed no significant abnormalities except that the patient was underweight. Complete blood count and flocculation reaction for syphilis were normal. The urine was milky in appearance and contained 127.3 mg. of fat and 500 mg. of sugar per 100 cc. Fasting blood sugar and glucose tolerance reactions were normal; however, the urine collected at 30 minute intervals contained sugar and this was regarded indicative of renal glycosuria. Cystoscopic examination and retrograde pyelography were not done. Microfilariae were not found in the blood.

**Case 2.** A 30 year old white woman, of German-Jewish extraction, was seen at the clinic in August, 1927. Her residence was Illinois and she had traveled in Missouri and Kentucky. Six months prior to her coming to the clinic, sudden severe pain had developed in the right renal region. This pain persisted for 2 hours and spontaneously disappeared with no recurrence. No other symptoms were present but within 1 week she first noted the presence of milky urine. Since onset, the milky urine had been present only in the morning. Physical examination did not reveal any significant abnormalities. Complete blood count was normal. The urine was milky and contained 100 mg. of

fat per 100 cc. Erythrruria and pyuria were graded 1+ (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition). The value for the total lipoids was 421 mg. per 100 cc. of plasma. The values for blood urea, uric acid, creatinine and serum protein were normal. Microfilariae could not be demonstrated in the blood. Cystoscopic examination did not reveal any point of entrance of chyle into the bladder, and the urine from both ureters was clear.

**Case 3.** A 58 year old white woman was seen at the clinic on several occasions between 1930 and 1934, at which time the results of general examinations were essentially negative except that they revealed a static type of arthritis. Her residence was Minnesota but she had traveled extensively throughout the southern part of the United States and in Egypt. Eight months prior to her last visit to the clinic, the patient had first noted the appearance of milky urine. There were no symptoms referable to the urinary tract. Physical examination did not reveal any significant abnormalities. Complete blood count was normal. The urine contained 25 pus cells per high power field. The values for blood urea and uric acid were normal. On cystoscopic examination, milky urine was seen to spurt from the left ureter and urine collected from the pelvis of the left kidney was milky in appearance and clotted soon after collection. A pyelogram of the left kidney questionably showed backflow. Microfilariae were not present in the urine or blood.

**Case 4.** A 41 year old woman, a resident of Canada, was seen at the clinic in March, 1935. She complained chiefly of upper lumbar back pain of 4 months' duration. Her past history was not significant and the extent of her travels was not recorded. Milky urine had been present for 1 month. An additional symptom of which she complained was recurrent swelling of the right leg for 4 months. Physical examination did not reveal any significant abnormalities except moderate obesity. Complete blood count was normal. The urine appeared

milky and contained 174 mg. of fat per 100 cc. Albuminuria and pyuria were each graded 1+. The values for blood urea, plasma cholesterol and serum protein were normal. Cystoscopic examination and a left retrograde pyelogram did not reveal any abnormalities.

Case 5. A 64 year old man of Chinese descent, who had been born in California, was at the clinic in 1936. He complained chiefly of passing thick, milky urine. In addition he had occasionally had mild dysuria and the urine clotted on standing. The symptoms had been noted first 7 years prior to his coming to the clinic. They had disappeared spontaneously 2 years later, but recurred 6 months before his examination at the clinic. Physical examination did not reveal any significant abnormalities. The urine was milky and contained 975 mg. of fat per 100 cc. Albuminuria and erythruia were each graded 3+. The plasma values for cholesterol and total lipoids were normal and the blood urea and blood sugar were within normal limits. The blood and urine were negative for microfilariae. On cystoscopic examination, milky urine spurting from the left ureteral orifice, but that from the right was clear. Not only did a retrograde pyelogram of the left kidney reveal pyelolymphatic backflow, but the injected contrast medium was excreted by the right kidney within 5 minutes. A subsequent retrograde pyelogram on the right was normal.

After this procedure, the chyluria did not recur until 6 months before the patient's second visit to the clinic, in 1941. A retrograde pyelogram at that time was negative. Urinalysis revealed milky urine containing 46 mg. of fat per 100 cc. Albuminuria was graded 4+ and erythru-Albuminuria was graded 4+ and erythru-uria 2+.

2 weeks prior to the patient's next visit, in June, 1946. Examination at that time revealed that the patient had lost some weight, but otherwise there had been no change. A left retrograde pyelogram revealed "marked lymphatic extravasation" medial to the kidney, as was seen originally in 1936.

The patient was last seen at the clinic

in August, 1947, when he returned because chyluria had persisted since the previous visit and he now was passing clots, which caused rather severe dysuria. These clots were noted to be numerous in the bladder on cystoscopy. Again, milky urine spurting only from the left ureteral orifice but a left retrograde pyelogram was negative.

Case 6. A 51 year old white man of Spanish extraction, whose residence was Puerto Rico, was examined first at the clinic in 1940, when a diagnosis of recurrent malaria was made. He returned to the clinic in July, 1946, complaining chiefly of aching in the left renal region of 1 year's duration and passage of "thick" urine often containing "chunks" of mucus intermittently for more than 6 years. There was no history obtainable of acute or chronic lymphangitis. Physical examination did not reveal any significant abnormalities other than a rather large right hydrocele. Laboratory examination revealed hemoglobin 14.0 gm. per 100 cc., erythrocytes 4,890,000 and leukocytes 7,400 per cu. mm., with eosinophilia noted on the blood smear. The flocculation reaction for syphilis was negative. A roentgenogram of the thorax was negative. Urinalysis showed a specific gravity which ranged from 1.014 to 1.021; albuminuria, grade 1+ to 3+; erythruia, grade 1+ to 3+; pyuria, grade 1+ (4 to 6 cells per high power field). The urine was milky and reported as "typical of chyluria." It contained 77 mg. of fat per 100 cc. On cystoscopy, a very minute papilloma about 4 mm. in diameter just posterior to the right ureteral orifice was noted and fulgurated. The urine spurting from the ureters seemed clear, but when ureteral specimens were examined, that from the right ureter contained 31 mg. and that from the left 11 mg. of fat per 100 cc. A left retrograde pyelogram revealed rather marked pyelolymphatic backflow.

Case 7. A 45 year old white woman was seen at the clinic in September, 1946. She complained chiefly of symptoms referable to the upper part of the gastrointestinal tract. Her residence was Puerto Rico and she was of Spanish descent. In



addition to the gastro-intestinal symptoms, she complained of the passage of milky urine intermittently since 1940. Urine of this type was passed usually in the first morning specimen, after which the urine was clear during the rest of the day. She gave a history of an acute episode of inguinal lymphadenitis associated with fever and red streaks on the right thigh at 14 years of age, but none since then. Microfilariae had never been demonstrated in the blood. The results of physical examination were negative. Laboratory examination revealed 14.4 gm. of hemoglobin per 100 cc., erythrocytes 4,840,000 and leukocytes 9,400 per cu. mm., with a normal differential count (1% eosinophils). The flocculation reaction for syphilis and a roentgenogram of the thorax were negative. The urine was milky in appearance and its specific gravity was 1.015. Albuminuria and pyuria were graded 1+. Blood and urine were negative for microfilariae.

Case 8. A 49 year old woman was seen at the clinic in February, 1947, having been referred to the clinic for post-operative (panhysterectomy) radium therapy, a diagnosis of carcinoma of the cervix having been made elsewhere. Her residence was British Guiana and it is recorded that she was of British, Spanish and Negro extraction. She complained of the presence of gallstones, which had been known for 5 years, and of the passage of milky urine for 30 years. She stated that she had had a "filarial infection" 30 years previously, but no further symptoms referable to this illness are recorded. Gross hematuria had been present on several occasions as well as the passage of "thick" urine, but there was no history of urinary obstruction. In 1911, a large left inguinal lymph node had been removed, supposedly for filariasis. Physical examination revealed enlarged, firm axillary and inguinal lymph nodes, absent cervix, uterus and adnexa (surgical) and atrophy of the right calf (proved to be secondary to palsy of the right sciatic nerve 16 years previously). Laboratory examination revealed 14.0 gm. of hemoglobin per 100 cc., erythrocytes 4,500,000 and leukocytes 5,700 per cu. mm. The

flocculation reaction for syphilis was negative. The urine was milky in appearance. Albuminuria was graded 4+ and erythru-ria 3+. A roentgenogram of the thorax was negative. A cholecystogram revealed the presence of gallstones. Blood and urine were negative for microfilariae. Examination of cervical tissue (removed elsewhere) by one of the pathologists at the clinic revealed squamous-cell epithelioma, grade 4 (Broders' method). Further investigation of the chyluria was not carried out in view of the necessity for prime attention to the pelvic lesion.

Case 9. A 34 year old white woman was seen at the clinic in July, 1943. She complained chiefly of having passed white urine for 3 months. Her residence was Illinois, but her birthplace and travels were not recorded. In 1937, she had had an episode of urinary obstruction relieved by right ureteral catheterization, the exact cause of the obstruction being undetermined. There had been no symptoms referable to the urinary tract since that time or since she had first noted the presence of milky urine. In 1941, an active pulmonary tuberculous lesion was discovered, for which she was hospitalized from January, 1942 to April, 1943, when the lesion was said to be arrested. Her sputum had been positive for acid-fast organisms. Physical examination did not reveal any significant abnormalities. Laboratory examination revealed 13.1 gm. of hemoglobin per 100 cc., erythrocytes 4,590,000 and leukocytes 4,500 per cu. mm. The specific gravity of the urine was 1.016. Albuminuria was graded 3, erythru-ria 2 and pyuria 3. The flocculation reaction for syphilis was negative. A roentgenogram of the thorax showed a lesion of the right upper lobe suggestive of tuberculosis. Cultures of urine were negative. No acid-fast organisms were found on examination of the urine or sputum. On cystoscopy, milky urine spurted from the left ureteral orifice and on retrograde pyelography there was suggestive pyelovenous backflow from the tip of the upper calix of the left kidney.

Case 10. A 59 year old white man was seen at the clinic in August, 1947. He complained chiefly of cloudy urine.

The patient was of Spanish-Cuban extraction, born in Key West, Florida. He lived in Florida until the age of 23 years and has lived in Brooklyn, New York, since that time. His only residence outside of the United States was in 1946 for 1 month in Mexico City. His first passage of cloudy urine had been in 1936 and had been accompanied by chills, temperature up to 102° F. and pain and swelling of both knees of 3 to 4 months' duration. No further milky urine was noted until 1946, when there was recurrence of symptoms as before, plus swelling of ankles and all proximal phalangeal joints of hands as well as redness and pain over the "vessels" of both lower legs. The milky urine persisted for 3 to 4 weeks, whereas the other symptoms subsided in 3 to 4 days. The patient was then well until 1 week prior to his examination at the clinic, when there was recurrence of cloudy urine, in which he noted "clots of mucus," and mild arthralgia in knees and hands.

Physical examination revealed bilateral inguinal hernias with an incisional (previous herniorrhaphy) hernia in the left lower quadrant of the abdomen; enlargement of the prostate, grade 2; and moderate pitting edema of both ankles. Laboratory examination revealed 15.6 gm. of hemoglobin per 100 cc., erythrocytes 4,670,000, and leukocytes 5,300 per cu. mm., with 4.5% eosinophils on differential count. The Kline, Kahn, Hinton and Kolmer reactions were negative. The urine was milky in appearance with a specific gravity from 1.017 to 1.025. Albuminuria was graded 4+, erythruia

3+ to 4+ and pyuria 1+ (4 to 20 cells per high power field). A roentgenogram of the thorax revealed torsion of the aorta. The concentration of urea was 30 mg. per 100 cc. of blood, that of uric acid 5.3 mg. per 100 cc. of serum, that of fasting blood sugar 168 and 86 mg. per 100 cc., that of cholesterol 247 mg. per 100 cc. of plasma, that of fatty acids 403 mg. per 100 cc. of plasma, that of total lipoids 650 mg. per 100 cc. of plasma, and that of protein 5.8 gm. per 100 cc. of serum. Serum sulfate, calcium and phosphorus were within normal limits. Blood and urine were negative for microfilariae. On cystoscopy, clear urine was seen to spurt from the right ureteral orifice, and milky urine from the left. The urine contained 402 mg. of fat per 100 cc. on the first examination. After two days of low fat diet, the urine contained 100 mg. of fat per 100 cc. One hour after ingestion of 16 fluid-ounces (473 cc.) of cream, the fat content of the urine was 170 mg. per 100 cc.; after 3 hours, 540 mg. per 100 cc.; after 4 hours, 570 mg. per 100 cc.; after 5 hours, 988 mg. per 100 cc. (Fig. 1).

**Summary.** We have reported 10 cases of chyluria encountered at the Mayo Clinic. The etiology and pathogenesis of chyluria are discussed. Chyluria is rare, but it is not a widely recognized entity, and should be considered in a differential diagnosis, along with pyuria, phosphaturia and lipuria, whenever a patient complains of milky, cloudy or white urine.

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# RELATION OF BODY WEIGHT AND FAMILY HISTORY OF HYPERTENSIVE DISEASE TO BLOOD PRESSURE LEVELS IN UNIVERSITY STUDENTS

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It is generally accepted that overweight is a factor in the production of hypertension. Short and Johnson<sup>1</sup> of the Life Extension Institute compared the blood pressures of 2858 overweight men and 658 men of normal weight whose average age was 40 years. In their series overweight appeared to be a factor in causing an increased incidence of hypertension. This effect was more marked in the diastolic pressures than the systolic.

TABLE 1. MEAN SYSTOLIC BLOOD PRESSURES BY HEIGHT-WEIGHT PER CENT AND AGE—MALE

<i>Age</i>	<i>Height-Weight %</i>	<i>No. Cases</i>	<i>Mean Systolic Pressure</i>	<i>S.E.</i>
20 and Under	Under 80%	155	118.7	±.1143
	80-89%	2375	119.5	±.0260
	90-109%	14915	121.7	±.0104
	110-119%	2841	124.1	±.0241
	120% and over	1424	126.7	±.0366
	Total	21710	122.1	
21-30	Under 80%	228	117.2	±.0745
	80-89%	2501	118.9	±.0230
	90-109%	14001	122.0	±.0090
	110-119%	2789	124.0	±.0220
	120% and over	1153	125.6	±.0357
	Total	20672	122.0	
31-40	Under 80%	28	109.5	±.1989
	80-89%	175	117.4	±.0870
	90-109%	717	120.9	±.0442
	110-119%	155	123.1	±.1042
	120% and over	62	123.7	±.1602
	Total	1137	120.6	
41 and Over	Under 80%	10	110.5	±.4050
	80-89%	42	120.7	±.2332
	90-109%	171	123.4	±.1119
	110-119%	41	125.0	±.2010
	120% and over	17	122.7	±.2528
	Total	281	122.8	
All Ages	Under 80%	421	117.1	±.0617
	80-89%	5093	119.1	±.0170
	90-109%	29804	121.8	±.0071
	110-119%	5826	124.0	±.0161
	120% and over	2656	126.1	±.0254
	Total	43800	122.0	

Hartman and Christ<sup>4</sup> studied the records of 2042 consecutive patients over 15 years of age at the Mayo Clinic. In about an equal number of men and women they found a consistent rise in the mean systolic blood pressures with an increase in weight. The mean diastolic pressures were found to increase with weight in women only. Alvarez,<sup>1</sup> Gager,<sup>3</sup> Symonds<sup>6</sup> and others have also reported studies showing this same general relationship between overweight and blood pressure.

In an earlier paper<sup>2</sup> the relation between age and mean blood pressure levels for 43,800 men and 31,458 women was reported by us. The group was composed largely of University students with an average age of 21 years. The blood pressure readings of this same group of over 75,000 students

have been correlated with height-weight % to determine what relationship there may be in young adults between body weight and blood pressure levels.

The height-weight % for each person in the group was computed according to the Medico-Actuarial tables. In the following discussion, the term weight is used to designate the height-weight % rather than actual body weight. Five weight groups were selected, the lowest including those persons falling below 80% of the standard, and the highest those 120% or more of the standard. In this same group of individuals,<sup>2</sup> it had been shown that in women the mean systolic blood pressure increased with age. In order to minimize the age factor in determining the effect of weight on

TABLE 2. MEAN SYSTOLIC BLOOD PRESSURES BY HEIGHT-WEIGHT PER CENT AND AGE—FEMALE

<i>Age</i>	<i>Height-Weight %</i>	<i>No. Cases</i>	<i>Mean Sys- tolic Pressure</i>	<i>S.E.</i>
20 and Under	Under 80%	362	107.6	±.0684
	80-89%	3383	107.8	±.0209
	90-109%	12106	109.1	±.0110
	110-119%	1862	111.6	±.0284
	120% and over	1086	115.0	±.0397
	Total	18799	109.4	
21-30	Under 80%	367	111.0	±.0570
	80-89%	2571	111.3	±.0214
	90-109%	6610	112.9	±.0135
	110-119%	939	114.2	±.0363
	120% and over	542	117.5	±.0531
	Total	11029	112.8	
31-40	Under 80%	83	113.4	±.1599
	80-89%	315	114.8	±.0738
	90-109%	699	115.9	±.0469
	110-119%	80	118.4	±.1364
	120% and over	85	121.1	±.1557
	Total	1262	116.0	
41 and Over	Under 80%	18	128.4	±.4657
	80-89%	77	121.0	±.1577
	90-109%	206	124.2	±.1264
	110-119%	37	127.5	±.3285
	120% and over	30	138.8	±.4869
	Total	368	125.3	
All Ages	Under 80%	830	110.1	±.0450
	80-89%	6346	109.7	±.0150
	90-109%	19621	110.8	±.0086
	110-119%	2918	112.8	±.0227
	120% and over	1743	116.5	±.0328
	Total	31458	111.0	

blood pressure, 4 age groups were established. The mean systolic blood pressure of each of the 5 weight groups within each of the 4 age groups was computed (Table 1).

In men the mean systolic blood pressures increase as the weight increases in every age group except in the group 41 and over where the number of cases is small. These increases are statistically significant. The same trend in mean systolic blood pressures with increase in weight was found in women with the exception again in the small group over 40 years of age (Table 2). When all ages are combined this same general trend is evident.

There is not the same definite relationship between the weight and the mean diastolic pressures as that seen in the systolic pressures. In men in

the ages between 21 and 40 there is a significant increase in mean diastolic pressure with increasing weight. This is not found in the group under 20 years of age or that over 40 (Table 3). In women there is even less correlation between the diastolic pressures and weight. The only age group showing significant differences in the diastolic pressures and weight increase is the 31 to 40 years (Table 4). Short and Johnson<sup>5</sup> found a similar increase in the mean diastolic pressures with increase in weight in men. Hartman and Christ,<sup>4</sup> however, in their series found no correlation between weight and the mean diastolic pressures in men but did find an increase in the diastolic pressures with increased weight in women.

In order to determine the relative effects of age and weight on both sys-

TABLE 3. MEAN DIASTOLIC BLOOD PRESSURES BY HEIGHT-WEIGHT PER CENT AND AGE—MALE

Age	Height-Weight %	No. Cases	Mean Sys- tolic Pressure	S.E.
20 and Under	Under 80%	155	73.9	±.9837
	80-89%	2375	72.7	±.2209
	90-109%	14915	72.6	±.0906
	110-119%	2841	73.7	±.2083
	120% and over	1424	75.2	±.2973
	Total	21710	72.9	±.0748
21-30	Under 80%	228	74.2	±.6589
	80-89%	2501	74.9	±.1926
	90-109%	14001	76.0	±.0831
	110-119%	2789	77.5	±.1871
	120% and over	1153	79.7	±.3002
	Total	20672	76.3	±.0686
31-40	Under 80%	28	72.0	±1.3000
	80-89%	175	75.8	±.7256
	90-109%	717	78.3	±.3493
	110-119%	155	80.5	±.7774
	120% and over	62	81.0	±.9151
	Total	1137	78.2	±.2800
41 and Over	Under 80%	10	77.5	±3.1781
	80-89%	42	80.0	±1.5504
	90-109%	171	81.6	±.8258
	110-119%	41	84.0	±1.5407
	120% and over	17	81.6	±2.3181
	Total	281	81.5	±.6290
All Ages	Under 80%	421	74.0	±.5225
	80-89%	5093	74.0	±.1435
	90-109%	29804	74.6	±.0616
	110-119%	5286	75.7	±.1404
	120% and over	2656	77.3	±.2121
	Total	48800	74.7	±.0510

tolic and diastolic pressures, the mean pressures for each weight group by ages is shown graphically in Figure 1. In men under 40 years of age, increased weight is associated with a higher mean systolic pressure, although in no weight group does age seem to influence the systolic pressure levels except after 41 years of age. In women, however, both increased weight and age are factors in producing higher systolic pressures.

There is an upward trend in the

guarding a family history of hypertension and cerebral hemorrhage. It seemed of interest to determine whether there were any differences in the mean systolic pressures of those individuals with a history of hypertension or cerebral hemorrhage in their families and in those with no such history. These data are presented in Tables 5 and 6. The mean systolic pressure in both men and women in those with no family history of hypertensive disease is lower than those with

TABLE 4. MEAN DIASTOLIC BLOOD PRESSURES BY HEIGHT-WEIGHT PER CENT AND AGE—FEMALE

<i>Age</i>	<i>Height-Weight %</i>	<i>No. Cases</i>	<i>Mean Sys- tolic Pressure</i>	<i>S.E.</i>
20 and Under	Under 80%	362	67.6	± .5843
	80-89%	3383	67.0	± .1903
	90-109%	12106	67.7	± .0996
	110-119%	1862	68.9	± .2536
	120% and over	1086	71.0	± .3461
	Total	18799	67.9	± .0806
21-30	Under 80%	367	71.9	± .4968
	80-89%	2571	71.4	± .1934
	90-109%	6610	72.1	± .1187
	110-119%	939	73.4	± .3178
	120% and over	542	75.3	± .4310
	Total	11029	72.2	± .0927
31-40	Under 80%	83	72.8	± 1.1782
	80-89%	315	74.5	± .3326
	90-109%	699	75.4	± .3746
	110-119%	80	77.6	± 1.1937
	120% and over	85	78.4	± 1.1658
	Total	1262	75.3	± .2879
41 and Over	Under 80%	18	83.9	± 2.8839
	80-89%	77	76.8	± 1.1156
	90-109%	206	79.2	± .9772
	110-119%	37	80.7	± 1.8470
	120% and over	30	87.2	± 2.9414
	Total	368	79.7	± .6970
All Ages	Under 80%	830	70.4	± .3766
	80-89%	6346	69.3	± .1360
	90-109%	19621	69.6	± .0775
	110-119%	2918	70.8	± .2015
	120% and over	1743	73.0	± .8682
	Total	31458	69.8	± .0616

mean diastolic pressures of both men and women for each height-weight group as the age increases. This is more marked in women than in men (Fig. 1).

Information was available in the health records of these students re-

such a history. While these differences are statistically significant, they are not very striking. Even in those individuals in whose families instances of both hypertension and cerebral hemorrhage had occurred, the mean systolic pressures were little different.

Summary. 1. The relation of body weight and family history of hypertensive disease to blood pressure levels in 75,258 students examined at the University of Minnesota has been studied.

2. In both men and women, the mean systolic blood pressures were found to rise as the weight increased in each age group through 40 years of age.

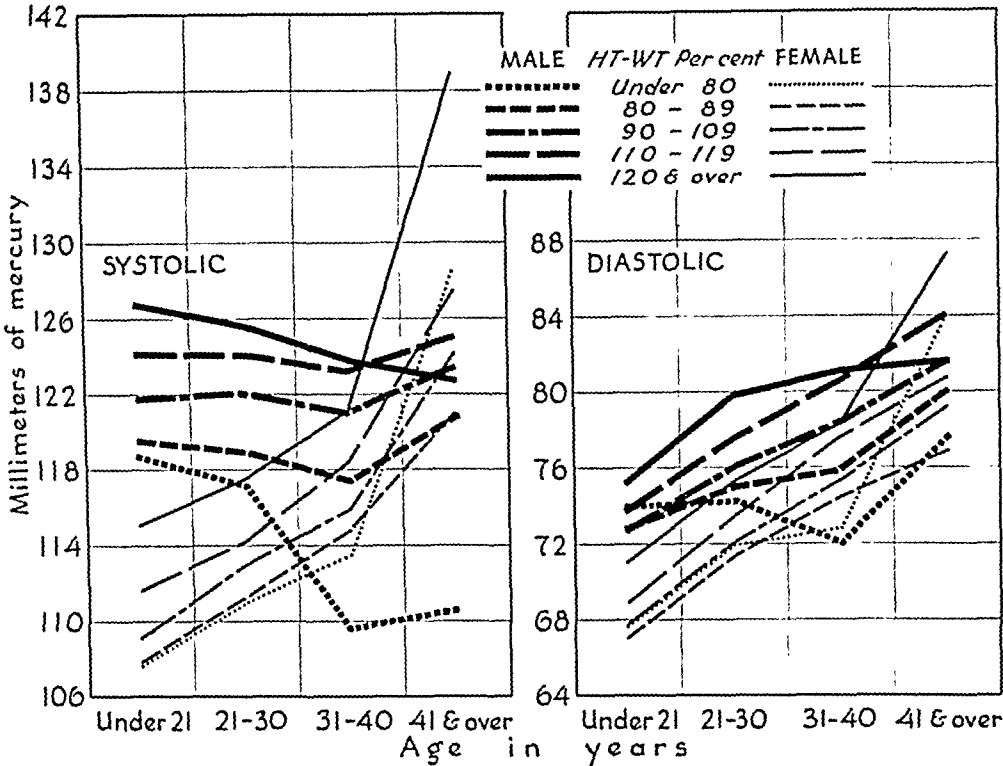


Fig. 1.—Mean systolic and diastolic blood pressure for 5 weight groups by age.

TABLE 5. MEAN SYSTOLIC BLOOD PRESSURES ACCORDING TO FAMILY HISTORY OF HYPERTENSIVE DISEASE—MALE

Family History of	Number of Cases	Mean Pressure	Standard Error
Cerebral hemorrhage	6985	122.2	± .1483
Hypertension	10559	122.8	± .1208
Cerebral hemorrhage and hypertension	2781	122.6	± .2317
Neither	29037	121.8	± .0728

TABLE 6. MEAN SYSTOLIC BLOOD PRESSURES ACCORDING TO FAMILY HISTORY OF HYPERTENSIVE DISEASE—FEMALE

Family History of	Number of Cases	Mean Pressure	Standard Error
Cerebral hemorrhage	6609	111.7	± .1523
Hypertension	8601	111.6	± .1342
Cerebral hemorrhage and hypertension	2814	112.8	± .2347
Neither	19062	110.7	± .0883



TABLE 7. MEAN SYSTOLIC BLOOD PRESSURES IN PERSONS WITH ABNORMALITIES OF CARDIAC STRUCTURE OR FUNCTION—MALE

<i>Persons with</i>	<i>No. of Cases</i>	<i>Mean Pressure</i>	<i>Standard Error</i>
Congenital cardiac defect, valvular defect, or cardiac hypertrophy	291	129.9	$\pm .9831$
Tachycardia only	1637	128.6	$\pm .3685$
No evidence of cardiac abnormality	11872	121.7	$\pm .0592$
Total	43800	122.0	$\pm .0592$

TABLE 8. MEAN SYSTOLIC BLOOD PRESSURES IN PERSONS WITH ABNORMALITIES OF CARDIAC STRUCTURE OR FUNCTION—FEMALE

<i>Persons with</i>	<i>No. of Cases</i>	<i>Mean Pressure</i>	<i>Standard Error</i>
Congenital cardiac defect, valvular defect, or cardiac hypertrophy	207	117.2	$\pm 1.1663$
Tachycardia only	1777	116.8	$\pm .3265$
No evidence of cardiac abnormality	29474	110.7	$\pm .0700$
Total	31458	111.0	$\pm .0693$

3. There was less effect of overweight on the mean diastolic pressures. In men in the age groups between 21 and 40 there was a significant rise in the mean diastolic pressures as the weight increased. In women, this relationship was seen only in the 31 to 40 age group.

4. In men up to 40 years of age, overweight rather than age seemed to

be an important factor in producing higher systolic pressures, while in women, both weight and age seemed to exert an influence on systolic pressure levels.

5. A family history of hypertensive disease was associated with slightly higher mean systolic pressures in both men and women.

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# THE CONTROL OF CIRCULATORY STASIS BY THE ELECTRICAL STIMULATION OF LARGE MUSCLE GROUPS

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THERE is little need these days to remind readers of the value of early movement after operation as a preventive of venous thrombosis and pulmonary infarction. Many patients however fear or resent the attendant discomfort. In others, unconsciousness, weakness or senility may exclude active movement. In all of these cases passive movement might supply the answer, but passive movement and massage on a large scale in a big hospital with many surgical operations is expensive. Any other procedure that ensures movement of venous blood without discomfort should therefore be a welcome addition to post-operative treatment, not only to prevent venous thrombosis, but to avoid peripheral circulatory failure.

The physiological considerations involved are briefly as follows: Circulation is maintained by three sets of pumps strategically placed along the blood circuit, viz. the heart, the voluntary muscles and the diaphragm. One of the essentials for efficient cardiac activity is a mechanism for returning an adequate volume of venous blood to the heart. This is maintained by skeleton muscle contractions (muscle pump) and by the piston-like action of the diaphragm during respiration (respiratory pump). Increased muscular activity therefore automatically tends to increase cardiac inflow and output.

The various causes of circulatory failure include loss of blood volume, failure of cardiac, muscle or respiratory pumps and the loss of vascular tonus. Although a vast amount has been written concerning most of these, it is only in recent years that we have begun to appreciate the role of the muscle pump, particularly as regards stagnation of blood in the lower limbs and the relation of this condition to post-operative shock and thrombosis with pulmonary embolism.

Some years ago it occurred to us that such stasis might be overcome by the artificial induction of muscle activity, for instance, by rhythmical electrical stimulation.

Since thrombi form most often in the legs, especially in the veins of the calf muscles, and leg muscles are the most readily accessible for electrical stimulation, we decided to confine our work to this area. Preliminary observations, herein reported, were made on that form of peripheral circulatory stasis and failure which is so readily induced by the force of gravity in certain subjects when suspended or lying immobile at an angle of 70 degrees from the horizontal (gravity shock or orthostatic circulatory insufficiency). The evidences of this state are an increase of heart rate and diastolic pressure, a decrease of pulse pressure and systolic pressure, together with some pallor, sweating and distress. The application

of the method to the treatment of traumatic shock and the prevention of post-operative thrombosis in this hospital will be recorded on another occasion. Our results so far are distinctly encouraging.

**Methods.** 1. *Production of stasis.* Circulatory stasis in the lower extremities was produced by the technique of "gravity shock" caused by the passive maintenance of a 70° angle from the horizontal by a subject on a tiltboard. The subjects had previously been found sensitive to this procedure and trained for complete relaxation and immobility.

2. *Source and type of electric current.* Passive muscular contractions in the thigh and calf were induced by a sinusoidal current (surging interrupted direct current with alternating polarity) from a Burdick Morse Wave generator M-210 at an intensity and frequency comfortable to the individual subject. This was usually at 20 to 30 milliamperes intensity and at a rate of 18 to 20 contractions per minute.

3. *Electrodes.* In the early experiments, the dispersive electrode, applied to the lumbo-sacral region, consisted of a thick stockinette girdle soaked in warm saline with a Crooke's metal contact. This was covered with rubber sheeting and held in place by a many-tailed surgical binder. The active electrodes were spiral muslin binders of fourfold thickness applied damp and as warm as tolerated from the ankle to groin. Half-inch ribbons of Crooke's metal were spiraled the full length of the binders and the whole covered with oiled silk held in place with ace bandages.

In later experiments, the dispersive electrode consisted of a thick square Burdick electrode pad 10 x 10 inches, thoroughly moistened with warm normal saline and held firmly in place over the lumbo-sacral region with a many-tailed binder. The active electrodes were similar rectangular pads, 3 x 12 inches each, applied to the dorsal surface of the calves and held with binders of dental dam rubber. Bifurcated and single leads connected the active and dispersive electrodes respectively to the generator.

4. *Procedures.* Pulse rates were determined at the radial artery on one arm and blood pressures (with a mercury or an aeroid manometer) on the other arm at one minute intervals. Circulation times were determined by the sodium dehydrocholate method. Since ankle to tongue time determinations were obviously impractical, antecubital to tongue determinations were made on the assumption that if our experimental procedures resulted in significant changes in the blood pressure of the radial artery, these changes would be reflected in similar variations in circulation time in the arm. In order to demonstrate any alterations in the velocity of venous return, the circulation time of the subject during gravity shock was compared with that of the same subject under the influence of muscle stimulation in otherwise identical circumstances.

**Experimental observations.** The subjects were healthy adults from 23 to 58 years of age. Thirty-two experiments were made.

All experiments were preceded by a 30 minute stabilization period, with the subject lying horizontal on the tilt-board in a warm, quiet and darkened room. After 10 minutes of basal observations, the subject was passively tilted to a 70° angle and maintained in that position during the period of observations.

1. *Controls* (i.e. not receiving electrical stimulation) were held at the critical angle until symptoms of gravity shock occurred. These usually became manifest when the pulse pressure had dropped to  $\frac{1}{3}$  or  $\frac{1}{4}$  of the basal level. The time varied from 10 to 50 minutes. Return to the horizontal position brought about prompt and complete recovery. Fig. 1 shows a typical gravity shock reaction.

2. *Intermittent Electrical Stimulation.* In these cases, gravity shock symptoms were allowed to develop before the introduction of muscular contractions by electrical stimulation. Bouts of alternating stimulation and

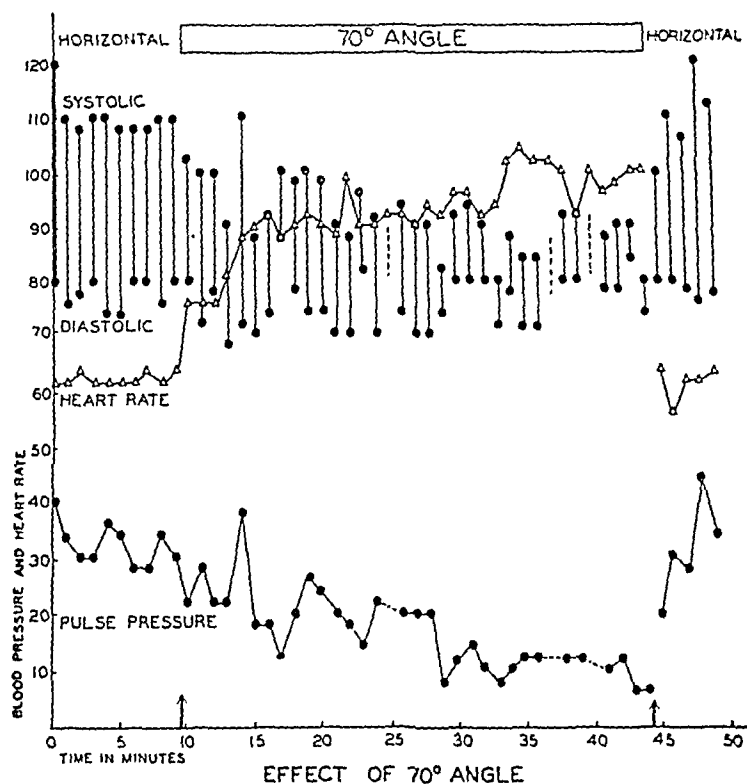


Fig. 1.—Showing the fall of pulse pressure and rise of heart rate induced by gravity in certain subjects when immobilized at an angle of 70° from the horizontal (gravity shock).

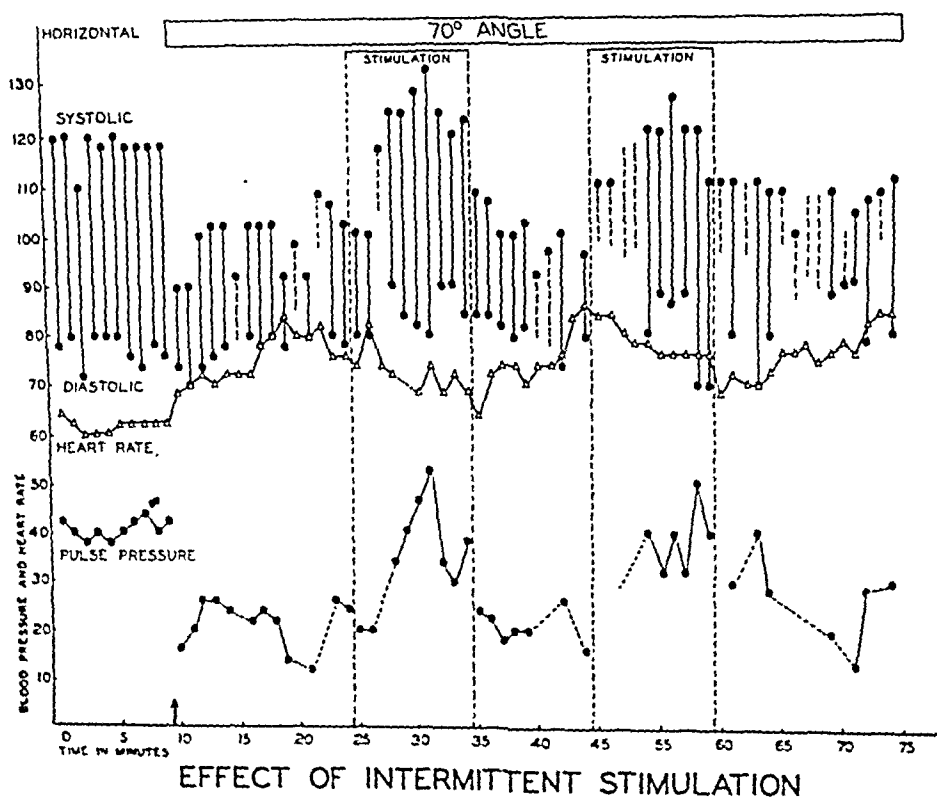


Fig. 2.—Showing the alterations in pulse pressure and heart rate in gravity shock and their restoration to normal during 2 periods of rhythmical muscle stimulation.

rest caused corresponding periods of recovery and relapse (Fig. 2).

3. *Continuous Electrical stimulation.* When electrical stimulation with accompanying contractions was instituted before tilting to the 70° angle and continued for the duration of the experiment, no signs of gravity shock developed.

4. *The circulation time*, determined during the period of circulatory stasis immediately preceding the "blackout" of gravity shock, was abnormally prolonged in all subjects. When however the experiments were repeated under identical circumstances, except that rhythmical muscle stimulation was maintained throughout, the circulation times were shortened to within normal limits (Table I).

changes in circulation time from antecubital fossa to tongue, as illustrated in four subjects.

Objection might of course be made that the reversal of the signs of gravity shock might be the result of emotional disturbances consequent to the mild discomfort of the electrical treatment. When however the type of current employed was one that produced similar discomfort without motor response, the course of gravity shock was unaffected.

**Conclusions.** A simple method of aborting or preventing the peripheral circulatory failure of gravity shock has been described.

The method is now being applied in this hospital: (a) in the treatment of traumatic shock, and (b) as a pre-

TABLE 1.  
Circulation Times (antecubital fossa to tongue)

Subject	In gravity shock at 70°	During electrical stimulation at 70°
F.L.A.....	24 sec.	16 sec. (right arm)
	15	7 (left arm)
M.K.C.....	27	16
	27	14
E.N.D.....	41	28
B.J. ....	30 plus	28

**Discussion.** Rhythmical electrical stimulation, applied to the muscles of the lower extremities of a subject in gravity shock, not only arrests the fall of pulse pressure and acceleration of heart rate, but rapidly restores them to normal. When the stimulation was introduced before the patient was subjected to the hydrostatic effects of gravity, the symptoms and signs of gravity shock are prevented completely.

That the peripheral circulation is retarded during gravity shock, and restored to normal by electrical stimulation, is shown by the corresponding

ventive of post-operative shock, venous stasis and thrombosis. To date, some 60 patients have been treated, but these numbers are too small to warrant conclusions. It is hoped, however, that the method will be tried and reported in other hospitals.

We are greatly indebted to the Burdick Corporation of Milton, Wis. for their generous gifts of a M-210 generator (now replaced by small portable model) and for technical help and advice, and to Dr. F. A. Hellebrandt, chief of the Baruch Center of Physical Medicine, for her active cooperation in all phases of the work.

\* This subject had to be returned to the horizontal position before the end-point was reached.

# ANTHRAX: 36 HUMAN CASES OF THE EXTERNAL TYPE TREATED SUCCESSFULLY WITH PENICILLIN

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HUMAN anthrax is a disease for which no active prophylaxis has yet been developed. The prevention of this disease is, for the most part, dependent upon the control of the infection in animals and the employment of general hygienic and sanitary measures. As the disease in humans is contracted through the handling of infected animals and their products, it is seen principally as an occupational disease in veterinarians and workers in wool and leather industries. Reports of the Philadelphia Health Department indicate that the incidence of anthrax in this city shows no tendency to decrease. In the period from 1904-1947 there were reported to the Philadelphia Health Department 433 cases with 50 deaths, a mortality of 11.5%. The source of contact in these cases was traced to imported hides, skins, wool, hair or their products<sup>3</sup>. In 5 patients, a store owner, the wife of a hide dealer, a machinist, and 2 unemployed persons, the source of infection could not be discovered.

Great advances have been made in the treatment of this disease since the use of specific antiserum was reported by Marchoux in 1895 and by Sclavo in 1903. Bacteriophage was employed by Villega Ruiz<sup>5</sup>, and Pijper<sup>4</sup> in 1926 reported the use of neoarsphenamine for the treatment of anthrax.

The present study deals with a series of 36 consecutive patients who were treated with penicillin alone. The first 3 cases of this series were reported in a preliminary report in 1944<sup>2</sup>. The first

patient was treated on 11-1-43, and the last on 12-23-47.

## DISTRIBUTION OF PATIENTS ACCORDING TO SOURCE OF INFECTION

Wool .....	25
Goat Skin .....	4
Hides .....	3
Goat Hair .....	2
Horse Hair .....	2
	<hr/>
	36

The preponderance of infections in wool workers is apparent from the above table. The wool handlers include twisters, blenders, carpet yarn reelers, carpet burlers, spinners, winders, sorters, combers, and pickers. Other patients worked as trucker, hair doffer, machinist, shipper, stripper, and glazer.

## LOCATION OF LESION

Arm—lower arm .....	19
upper arm .....	2 21
Face .....	10
Neck .....	2
Shoulder .....	1
Chest .....	1
Back .....	1
	<hr/>
	36

The exposed parts of the body were most frequently affected. It is presumed that all cases, which were of the cutaneous type, were contracted by direct contact with contaminated material. In many instances the organism was probably inoculated into the skin or hair follicles by repeated irritation. Lesions on the forearm were more common in yarn twisters who carried skeins of yarn over the arm and in

spinners who carried the spools by the armload.

Twenty-one patients were males and 15 were females. There was no preference for sex except as the occupation was influenced by the requirement of special skills peculiar to the sex.

Because the disease is an occupational one, the patients are for the most part in the older age group, and age of the patient has otherwise no bearing on the incidence of the disease. The youngest was 18 years old; the oldest, 75 years. Social and economic factors as they affected employment over this period were factors which strongly influenced the distribution of patients by sex as well as by age.

The yearly distribution of cases was as follows: 1943-3 (Nov.-Dec.); 1944 -2; 1945-7; 1946-14; 1947-10.

A definite history of trauma was obtained in 3 cases. One patient who developed a lesion on the shoulder was a trucker who carried hides, another patient developed a lesion on the tip of the nose where oil drippings had traumatized the skin, and the third patient, the only one in this group with a multiple lesion, was struck with a block on the forehead where the anthrax infection later appeared.

DURATION OF DISEASE AT TIME OF  
ADMISSION TO HOSPITAL

Days	No. of Patients
1 .....	3
2 .....	5
3 .....	10
4 .....	7
5 .....	5
6 .....	3
9 .....	2
15 .....	1

The average duration of disease was 4 days before patients were admitted to the hospital. The average stay in the hospital was 14 days, the range was from 7 to 36 days.

**BACTERIOLOGY:** The discharge from the lesion was placed on a slide for

examination and plain blood agar culture tubes were inoculated, immediately on admission, then once daily until 2 successive negative smears and cultures were obtained. A blood culture was taken on each patient immediately upon admission.

RESULTS OF SMEARS AND CULTURES

Smear	Culture	%
Positive	Positive	52.7
Negative	Positive	19.4
Positive	Negative	11.1
Negative	Negative	16.6

Thus bacteriologic confirmation of the diagnosis was possible in 83.4% of the cases, and in the majority of the cases both smears and cultures were positive for anthrax bacillus. In the 6 cases (16.6%), where the diagnosis was not confirmed bacteriologically, the characteristic appearance of the lesion left no doubt as to the clinical diagnosis.

DAYS OF PENICILLIN TREATMENT NECESSARY  
TO RENDER CUTANEOUS ANTHRAX LESIONS  
BACTERIOLOGICALLY NEGATIVE

Days of Penicillin Treatment	No. of Patients
1 .....	9
2 .....	9
3 .....	9
4 .....	1
5 .....	1
6 .....	0
7 .....	1

Of the bacteriologically positive cases, 30% became negative 24 hours after treatment was instituted. The same number became negative after 48 hours and an equal number after 72 hours, so that a total of 90% of the cases had become negative after 72 hours of penicillin therapy. One patient who had negative smears and cultures for 6 days had a positive smear on the 7th day. Another patient who received 6 injections of sodium penicillin (total 150,000 units) before admission had negative smears and cultures on each examination, while

another patient who was treated with oral penicillin had positive smear and culture from the lesion when admitted to the hospital on the 15th day of disease. Blood culture in each case was reported sterile.

**TREATMENT:** The dictum of "hands off" was strictly followed. Except to obtain vesicular fluid for bacteriologic study, the lesions were not disturbed. A plain sterile dressing was used to cover the lesion, sometimes a bland ointment was used to prevent adhesion of the dressing. When possible, loose bandages or binders were used in preference to adhesive tape to secure the dressings. Because of the absence of pain it was difficult to rely on the patient voluntarily to immobilize the part involved. It was occasionally necessary to splint an extremity in order to discourage excessive motion.

Because of the absence of pain in this disease, it is rarely necessary to administer narcotics or analgesics. The location of the lesion in certain parts of the body where the subcutaneous tissue is sparse may cause considerable discomfort but never enough to be a serious problem. Edema is present in every case in a varying degree. When edema is in or near a vital structure such as the eye or neck, it may require urgent and concerted effort to abate it. In such instances it is easier to inhibit edema by the early and continuous application of cold to the part.

The only specific treatment employed in the group being reported was sodium penicillin solution. Except for the first 3 patients who received penicillin intravenously, penicillin was administered intramuscularly. The majority of the patients in this group were given between 100,000 to 200,000 units in a 24-hour period at 3 hourly intervals.

In most cases the lesions were regressing after the smears and cultures became negative on 2 successive days,

at which time treatment was discontinued. The first 3 cases of anthrax in this group apparently responded satisfactorily to doses which were much smaller than were used subsequently. The earlier cases received from 50,000 to 100,000 units in 24-hour period.

**Comment:** It was observed that in many cases, the lesions continued to spread and the edema increased for 24 to 36 hours even after treatment was begun. In the past when patients were treated with antiserum, this phenomenon was frequently observed. It was postulated that a reaction between the infection and the specific serum occurred which was manifested as an inflammatory reaction. It may be that such may also be the case when penicillin is employed. Another hypothesis which may explain the reaction is that the infective process is accelerated by the specific therapy so that the anthrax lesion proceeds along a definite pattern which eventually terminates in resolution of the lesion. The presence of a "tissue damaging factor" has been considered by some, so that the infection may progress to a fatal termination even though the cultures from the blood and lesion are sterile<sup>1</sup>.

It was not necessary to use adjunctive treatment for the patients herein reported. Specific anti-anthrax serum is not available commercially at the present time, but we contemplated the transfusion of any patient who did not respond to penicillin with immune whole blood which might be available from persons who have recently recovered from anthrax.

There were no untoward reactions to penicillin in our cases which warranted the cessation of its administration.

**Conclusions and Summary:** Thirty-six patients with uncomplicated cutaneous anthrax were treated with sodium



penicillin in doses from 100,000 to 200,000 units daily.

The cutaneous lesions became negative in 27 of 30 bacteriologically positive cases after 3 days of penicillin treatment.

Penicillin apparently has no direct or immediate effect on the tissue damaging factor of cutaneous anthrax.

Intramuscular penicillin may be safely used successfully to treat cutaneous anthrax.

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# AN EPIDEMIC OF TULAREMIA TRANSMITTED BY INSECTS IN SETTLEMENTS OF DEPORTATION, ASINO AND JAJA, SIBERIA, SOVIET RUSSIA: REPORT OF 121 CASES.

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THE knowledge of those forms of tularemia which are not common in America contributes to a better understanding of this disease. While a political deportee, the author had the opportunity to observe an uncommon and interesting epidemic outbreak of tularemia in Siberia, USSR. The data accumulated warrant publication, since no similar observation could be found in the American literature.

Tularemia is an American disease. It was first described here in rodents by McCoy and Chapin<sup>12,13</sup>, who also discovered the *Bacillus Tularensis*. Other early contributions to this subject also came from the United States; Wherry<sup>28</sup> reported the transmissibility of this disease to man, Francis<sup>5,6</sup> gave the classical description of this condition as it occurs in man and named it tularemia, Foshay<sup>2</sup> developed the diagnostic allergic reaction and introduced serum treatment for this disease. Subsequently tularemia was recognized in many other countries but the two most important reservoirs of this disease are still the United States and Soviet Russia.

There are great differences in the epidemiology and the clinical picture of tularemia in these countries. This becomes clear when the American literature<sup>2,3,5,6,9,11,12,13,22,23,27,28</sup> is compared with the Russian reports on the subject.<sup>1,8,10,15,21,24,25,26,29</sup>

The main animal reservoir of tularemia in the United States is composed of ground squirrels, cotton-tail rabbits, snow-shoe hares, and many other rodents. On the other hand the main source of infection in Soviet Russia consists of water-rats (*Arvicola amphibius*) and to smaller extent of ground-rats (*Arvicola terrestris*), muskrats and meadow-mice (*Microtus*), while rabbits, squirrels and hares play a far lesser role.

According to Foshay<sup>4</sup> more than 90% of human cases in the United States result from direct contact with infected rodents and their tissues, fluids and pelts. Since the seasonal distribution of tularemia in the United States depends on this factor, outbreaks of the disease occur from April to October when jack-rabbits are handled, November to January when cotton-tail rabbits are hunted, March to September when the disease is transmitted from rodents by ticks, and June to September, if the vector is *Chrysops Discalis* (Meyer<sup>14</sup>). In Soviet Russia the seasons of tularemia are as follows: April to June if the epidemic is due to rats; at this season the infected water-rats start to populate shores of the rivers after floods have subsided and are hunted by rat-hunters; late fall and winter, if the epidemic is epizootic among meadow-mice, which infect the grain placed in stacks; summer, if the epidemic is due to

\* The author, formerly connected with the Second Department of Medicine, Faculty of Medicine, University of Warsaw, Poland, was during World War II deported by Russians from Eastern Poland to Siberia (in June 1940). He worked there as a political deportee in the Hospital of the settlement Asino, Siberia, USSR, for 15 months until he was released at the outbreak of German-Russian hostilities.

transmission of tularemia by insect vectors.

The main vectors of tularemia in the United States are the following insects: the deer-fly (*Chrysops discalis*), stable fly (*Stomoxys calcitrans*) and wood- or dog-ticks (*Dermacentor andersoni* and *Dermacentor variabilis*). In Soviet Russia the following insects (besides those enumerated above) are considered capable of transmitting tularemia: mosquitoes (*Anopheles maculipennis*, *Culex apicalis*, *Aedes caspius*, and others), midges (*Chironimidae*) and small flies (Buffalo-gnats, *Simulia*).<sup>21</sup>

There are some distinct differences also in the clinical picture and mortality of tularemia in the United States and in Soviet Russia:

The chief type in both countries is the ulcero-glandular. While in the United States more than 90% of lesions are located on the upper extremity, in Russia only 65 to 70% of the cases show this localisation. The ocular form is much more frequent in the United States than in Russia. On the other hand the anginous form, which has been described many times in Soviet Russia, is practically unknown in the United States.

The pulmonary complications of tularemia are extremely rare in Soviet Russia but are very common in the United States. Because of the virulence of the American strain of *B. tularensis* and its affinity for the respiratory tract, the mortality in the United States was much higher than in Russia prior to the advent of streptomycin. According to the United States Public Health Service the American mortality rate was 5.6%. In Soviet Russia the mortality rate was approximately 1.0%.

Epidemic outbreak of tularemia in Asino and Jaja, Siberia. The settlements of deportation Asino and Jaja are situated in the province of Novosibirsk in the South Eastern corner of the great Western-Siberian Plain approximately at the 55th degree of East-

ern longitude and 58th degree of the Northern latitude. Asino lies about 100 miles to the North of Tomsk and forms the terminus of a railway branch running from this town to the North. Asino and neighbouring Jaja are situated within "tajga", that is, dense, low, leafy and coniferous woods. The settlements are surrounded with moors and swamps and lie at the Czulym river, which belongs to the basin of the great river Ob.

The basin of the river Ob has been known as a tularemic area since 1930, and scattered cases of tularemia have been noted among water-rat hunters and the native population working with rat-pelts. The water-rats are encountered in large amounts on the shores of the river Czulym and adjacent stagnant waters. Moreover, a few meadow-mice and field-mice as well as some hares and squirrels are encountered near inhabited places. Swarms of insects are found in this region. The meadows and woods are crowded with mosquitoes (*Culex*, *Aedes* and *Anopheles* varieties) as well as with *Simulia* and midges. Swarms of flies (*Musca domestica* and *Stomoxys calcitrans*) are found in close proximity to inhabited barracks and live-stock. *Chrysops discalis* is encountered infrequently on the shores of rivers and marshes; ticks are found only in the woods.

The average winter temperature is between -20° and -40°C. The average summer temperature in July is between 10° and 20°C. The summer of 1941 was, however, warmer than usual.

At that time the population of the settlement Asino was composed of 1840 Polish citizens, who in June, 1940, were forcibly deported to Siberia from Eastern Poland occupied by Russians at the outbreak of the World War II. The population of the adjacent settlement of Jaja, located only a few miles from Asino, consisted of 460 peasants deported from Poland at the same time,

and mostly of Ukrainian nationality. The population of other adjacent villages (Asino, Woronopasche, Feotistowka, Trichomirowka, Wozniesienko, Kalinowka, Nowikowka, Puszkino, Ilinskij, Tuistat, and others) consisted only of Russian peasants, most of whom had been transferred and deported to Siberia from the Russian Ukraine in the pre-war years.

The hospital of the settlement Asino was located in wooden barracks of the settlement Sosnowka, and belonged previously to one of the jail settlements of the "Tomasinlag"\*. It had a capacity of about 100 beds and took care of the entire Polish population of the settlements Asino and Jaja, as well as the Russian population of all the adjacent villages. The hospital had an out-patient department which was run by 6 deported Polish physicians, and several wards for infectious, medical, surgical and pediatric diseases, the staff of which was composed of 5 other deported Polish physicians. There were also a laboratory and a pharmacy. The activities of the Polish staff of doctors were controlled by Russian local District Health Authorities.

The Polish medical staff† took an active part in the observation and treatment of our tularemic patients. The Russian health authorities also helped us in our work.‡

One hundred and twenty-one cases of tularemia were observed in the hospital of Asino during July and August, 1941. There were 63 ambulatory patients (40 Russians and 23 Polish

citizens) and 58 hospital cases (28 Russians and 30 Polish citizens). There were 81 females (66.9%) and 40 males (33.1%). Their ages ranged between 6 and 63 years; 50 were under 20 years of age (among them 32 children below 15 years); 53 patients were between 20 and 40 years; 18 patients were above 40 years of age. More than half of the patients (63) were peasant or field workers. One fourth of the patients (30) were children going to the village public school. There were also among the patients 12 men who worked in the saw-mill of Asino, 14 watchmen, coachmen and clerks, and finally 2 children below school age.

Many other cases of tularemia occurred in the neighboring villages during July and August, 1941. This was evident from the information supplied by our patients. Without any doubt the 121 cases reported in this paper constituted only a part of a much larger epidemic of tularemia in this district. Since we had no access to the statistics of the Russian District Health Authorities, we were not able to ascertain the exact extent of the epidemic.

**Epidemiology.** Among the most striking and unusual features (even in Russia) of this epidemic were its massive and sudden outbreak, its very short duration, and its uniform type. Although scattered cases of the ulceroglandular form of tularemia were treated in the hospital during the period between July, 1940, and July, 1941, the true epidemic outbreak started within the first few days of July, 1941.

\* "Tomasinlag" is an aggregate of many camps of confinement and forced labor of the Tomsk-Asino District. It was run by NKVD (Russian Security Police) and was populated mostly by Russian political and criminal prisoners.

† The author wishes to express his deep appreciation for the work which was done by the Polish medical staff.

Dr. J. Ber helped us very much in collecting the epidemiologic data. The late Dr. J. Olecka, as well as Drs. Brunne and Szpigelman participated in the routine hospital work. Drs. Dzievulski, Fajman and Kadysiewicz observed the ambulatory patients and permitted us to review their cases. Mgr. Keiler did all the laboratory work.

‡ The Division of Infectious Diseases of the Medical Faculty of the University of Tomsk, headed by Prof. Minkiewicz, delegated an entomologist to the Settlement and supplied us with adequate amounts of tularemia antigen for agglutination tests and tularin for allergic tests. Prof. Minkiewicz visited the settlement and gave us clinical advice.

Dr. Litwinow, head of the Russian local District Health Authorities, brought us into contact with the Division of Infectious Diseases of the Medical Faculty of the University of Tomsk.

At this time 6 cases of tularemia were brought to the hospital. From then on, the number of cases increased rapidly, so that 11 more cases were admitted during the second 10 days and 19 new cases during the last 10 days of July, 1941. The peak of the epidemic was attained during the first 10 days of August, when 45 new cases were admitted. At this time our small hospital of 100 beds was practically filled to its capacity with tularemic patients. After the peak was reached, the epidemic subsided rapidly. During the second 10 days of August, 22 new cases were admitted and during the last 10 days of August only 6 new cases. During the first few days of September only 3 new cases were admitted, and finally the epidemic stopped as rapidly as it came. (During the epidemic, 9 ambulatory cases were observed in addition in the settlement; the dates of the beginning of the disease in these cases could not be determined).

The outbreak of the epidemic started apparently in the collective farms (kolchoz) Nowikowka and Foetistowka. Rapidly the settlement and village of Asino, as well as the settlement of Jaja were invaded.

The morbidity rate in Asino was 1.8%. Among the 1840 persons living in the settlement of Asino 33 contracted tularemia during these 2 summer months. The highest incidence of tularemia occurred, however, in the neighboring settlement of Jaja, where, out of 460 persons, 52 (11.3%) developed this disease within 50 days (from July 10, 1941 to August 30, 1941). There is no record in medical literature of tularemia in which the morbidity rate was as high as this one.

According to the epidemiologic investigations of the Public Health Authorities of the Novosibirsk Province, (Karpov<sup>10</sup>) and information obtained from the entomologist of Tomsk University, the main source of tularemia

in this area is always the water-rat (*Arvicola amphibius*). The water-rats leave their holes after floods, which in Siberia occur in May and June, and take refuge in the brushwood along the shores of the river. In 1941 an unusual number of dead water-rats were found on the shores of the Czulym river and adjacent stagnant waters. This could indicate an epizootic among these rodents in the summer of 1941.

Although most cases of tularemia in Soviet Russia are reported in connection with rat-hunting or working with rat-pelts, this direct mode of infection could not be accepted for our cases. All of our tularemic patients were asked about direct contact with rodents and all of them flatly denied any direct contact with water-rats, squirrels, rabbits or hares. Meadow-mice did not play any rôle in the Asino epidemic of tularemia. Usually, in such cases the stack of grain is infected by tularemic mice, and the tularemia bacilli are transmitted to man by inhalation of infected grain dust during thrashing, or by ingestion of bread made of infected grain. This indirect method of transmission occurs only in fall and winter, so that it does not apply to our cases. Moreover, the clinical features of our cases indicate another portal of entry for the infection.

Tularemia may also be transmitted to man in an indirect way. An insect acting as a vector bites infected rats and subsequently man. This method of infection is accepted in the United States and in Russia for occasional cases of tularemia. However, neither in the United States nor in Soviet Russia has there been published a report of an epidemic outbreak of this kind. The only report similar to this was made by Olin<sup>16,17</sup> in Sweden. He described an outbreak of tularemia among 115 peasants walking barefoot and bitten by mosquitoes in Gävleborg district in 1937.

In our epidemic the following facts indicate that tularemia was transmitted to man not directly from rodents, but by insects acting as vectors. (1) None of our patients had any direct contact with rodents. (2) One hundred fifteen cases out of 121 developed the ulceroglandular form of tularemia. The primary focus in 66.9% of the cases was situated on the lower part of the leg or on the foot. This excludes the direct way of infection from the rodents, in which case the hands are usually infected first. (3) The portal of entry of *B. tularensis* was uncovered at the time of the infection. This was true of the cases in which the primary focus was located on the face, neck, hands, arms, legs and feet. The adults worked in the fields and meadows making hay or in saw-mills with their arms and legs uncovered and often barefooted; the children walked to the village school without shoes. (4) The peak of the epidemic corresponded to the peak of the development of small insects in the Czulyk area (the end of July and August). (5) All the patients admitted frequent bites of small insects a few days before the outbreak of the disease.

These facts suggest that insects acted as vectors in this epidemic. It must be conceded, however, that no definite opinion has been established concerning the type of the insect responsible. The entomologist of Tomsk caught many types of insects encountered in the area of the epidemic and examined them for the presence of *B. tularensis*. Due to my unexpected departure from the place of deportation in September, 1941, I was unable to obtain the results of these examinations. However, since the examinations were made very late in the epidemic they would not have been very reliable.

The vector of this epidemic probably would not be found among the group of biting flies like *Chrysops* or *Stomoxys*, or among the ticks; the search for it

should be made among the small insects, like mosquitoes, midges or *Simulia*.

The following evidence suggests this conclusion: (1) None of the patients recalled having been bitten by a fly; the bite of *Chrysops* or *Stomoxys* is painful and cannot be overlooked. (2) Most of the patients did not notice the primary focus until their attention was called to it. (3) No ticks were seen by the patients, and such ticks are found only in woods or on live-stock in Siberia. When present, the ticks in Siberia (mostly *Ixodes persulcatus*) bite in May or June, but not in August, as exemplified by the early estival Siberian type of tick-encephalitis. (4) Most of the patients were bitten by mosquitoes while making hay or weeding potatoes. (5) Almost all the patients stressed abundance of mosquitoes and midges at their place of work. (6) Among 32 children below the age of 15 years, who habitually walked with uncovered legs and barefooted, 30 (93.7%) were bitten on the foot or lower part of the leg, and only 2 (6.3%) on the face or hand. On the other hand, of the 83 cases of ulceroglandular form of tularemia in adults 51 (61.4%) were bitten on the legs or feet, and 32 (38.6%) on the face, neck, hands or arms. The adults did not have their legs and feet regularly uncovered. This shows that insects responsible for transmission of tularemia bit first on the uncovered lower part of the legs. They bit the face, neck, hands, and arms only if legs were covered. This is typical for the mosquitoes. (7) The experiments of Philip, Davis and Parker<sup>20</sup> proved that the *Bacillus tularensis* could be transmitted by mosquitoes (*Aedes vexans*, *Aedes stimulans*, *Aedes canadensis*, *Aedes aegypti*, *Theobaldia incidens*) and that it could live in mosquitoes for several weeks. Moreover Olin<sup>18,19</sup> (suspecting mosquitoes as vectors of tularemia in his epidemic

outbreak in Sweden) was able to prove the presence of *B. tularensis* in *Aedes cinereus*, by the inoculation of an emulsion of these mosquitoes into guinea pig.

The possibility of transmission of tularemia also by midges (*Chironimidae*) or *Simulia* should be kept in mind because of the large swarms of these insects were present in the working places. Since these insects ordinarily bite higher (face, neck or arms), mosquitoes are the vectors of this epidemic deserving serious consideration.

**Serologic and Immunologic Tests.** Out of the 121 cases of tularemia, 114 were proven by serologic or allergic tests, or by both. A positive tularemic agglutination test in a titer higher than 1:100 was obtained in 79 cases; a positive allergic intracutaneous test

was noted in 8 cases in which agglutination was negative or was not done. In 27 other cases positive agglutination test and positive intradermal allergic test were obtained.

A positive *agglutination test* with tularemic antigen was found in 106 cases. In 92 the test was performed by a classical method, using the tularemic antigen supplied by the Tomsk University (suspension of *B. tularensis* killed with ½% formalin, containing 1 billion of *B. tularensis* per cc.). Dilutions of 1:50, 1:100, 1:200, 1:400, and at times 1:800 were used. Positive reaction in a minimal titer of 1:100 was accepted as evidence of tularemia. Among 92 cases which gave a positive agglutination reaction, in 17 the titer was 1:100, in 9, 1:200, and in 66 cases, 1:400 or 1:800.

Table 1

Time of occurrence of positive agglutination and allergic tests in some cases of tularemia observed during the epidemic in Asino.

Case No.	Agglutination reaction in serum for tularemia		Intracutaneous allergic reaction for tularemia	
	Day of illness	Result of the test	Day of illness	Result of the test
1	10	negative	11	positive
	20	positive in a titer 1:200		
13	10	negative	10	positive
	16	positive in a titer 1:400		
31	13	negative	12	positive
	20	negative		
	26	positive in a titer 1:400		
35	17	negative		
	25	positive in a titer 1:400		
48	13	negative	9	positive
	21	positive in a titer 1:400		

In most of our cases, corresponding to the observations of others, the agglutination test became positive only in the third week, and gradually increased in titer thereafter. The incidence of the positive agglutination test in the second week was only 47% (9 tests out of 19); and in the third week, 96.5% (83 tests out of 86). Typical findings, which illustrate the late positive agglu-

tionation reaction are listed in Table 1.

In addition to the 92 positive agglutination reactions, which were obtained by the classical method, in 14 other cases the simplified rapid micro-method of Minkiewicz was used.

One drop of blood is hemolysed on the slide by the addition of a drop of distilled water. Two drops of tularemic antigen containing 10 billion bacilli in 1 cc. are added

Table 2

Classification of clinical forms of tularemia which were observed during the epidemic outbreak in settlements Asino and Jaja.

Clinical forms of tularemia	Number of cases	Percentage
I. Oculo-glandular form	2	1.7
II. Anginal (tonsillar) form	3	2.5
III. Typhoid form	1	0.8
IV. Ulcero-glandular form	115	95.0
a. Primary focus located on the lower extremity. Swelling of the inguinal and femoral lymphglands.	81	66.9
b. Primary focus located on the upper extremity. Swelling of the axillary and epitrochlear lymphglands.	18	14.9
c. Primary focus located on the face or neck. Swelling of the cervical, submaxillary, supraclavicular or infraclavicular lymphglands.	16	13.2
Total	121	100.0

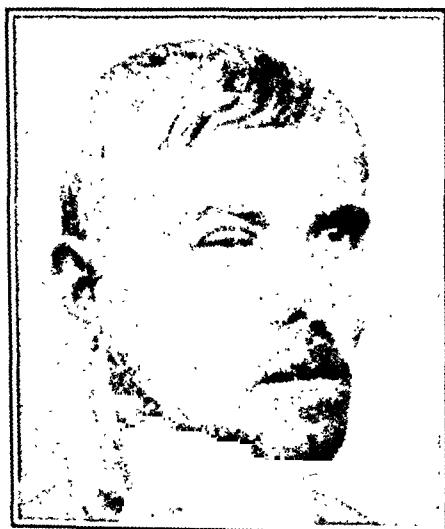


FIG. 1. Oculo-glandular form of tularemia.



FIG. 2. Anginal (tonsillar) form of tularemia.



and mixed thoroughly. Controls are made simultaneously with the same blood added with physiological salt solution, with paratyphoid, typhoid, and brucella antigen. Fine-grained or coarse-grained agglutination in absence of the agglutination with control solutions occurring 1 minute after the addition of the tularemic antigen is accepted as evidence of positive or strongly positive reaction.

The test of Minkiewicz in the third week of the disease gave 100% of positive results.

*Intradermal allergic tests* with 0.1 cc. of tularin were made in 43 clinically evident cases of tularemia. The tularin which was used consisted of tularemia bacilli killed by heating at 70°C and suspended in physiological salt solution; the tularin was added with 3% glycerin, and contained 10 million of *B. tularensis* in 0.1 cc.

Positive reactions were obtained in 35 out of 43 examined cases. In the third week of tularemia or later, the reaction was found positive as frequently as the agglutination reaction (12 positive tests out of 13). The advantage of the allergic intracutaneous test over the agglutination reaction was that it often detected the disease even in its earliest period. Out of 35 tests which were performed in the first 2 weeks, a positive response was obtained in 23, or in two thirds of the cases. Out of these 23 positive tests, in 15 the positive reaction was obtained at the end of the first week of the disease.

**Classification and Symptomatology.** All forms of tularemia, which are listed in the classification of Francis, were found in our epidemic. The classification of these 121 cases is tabulated in Table 2. The data listed in this Table show that the most common form of our epidemic of tularemia was the ulcero-glandular one, which was represented by 95% of cases. The remaining cases (5%) were composed of the oculo-glandular, the tonsillar and the typhoid forms of tularemia.

**OCULO-GLANDULAR, ANGINOUS (TONSILLAR) AND TYPHOID FORMS OF TULAREMIA:** The clinical picture of these forms was typical in our cases and did not show any unusual features.

The *oculo-glandular form of tularemia* was observed in 2 cases (Fig. 1). In these cases the primary focus was situated typically on the lower palpebral conjunctiva. Edema of the palpebral conjunctiva, chemosis, injection with subsequent ulceration, and sup-puration of conjunctiva were associated with lacrimation and pain in the eye. The preauricular, submaxillary and cervical lymph glands were swollen. The patients had moderate fever lasting for 7 to 10 days, followed by several weeks of low grade elevation of temperature. There were no signs of the involvement of central nervous system. The course of the disease was benign, and complete recovery occurred after several weeks. The intracutaneous allergic reaction and the agglutination test in serum were strongly positive.

The *anginous (tonsillar) form of tularemia* was observed in 3 cases (2 boys of 14 and 16 years of age and 1 woman 57 years of age). This form of tularemia is well known in Soviet Russia and is due to the drinking of water from collections of standing water or wells infected by water-rats or mice. All 3 patients admitted drinking such water when making hay.

All patients showed a typical primary focus in form of an ulceration on the tonsils with subsequent necrotic or diphtheritic ulcer. The latter had a very protracted course with very slow healing, accompanied by a characteristic enlargement of the regional submaxillary and cervical lymph glands, which were very painful at the outset. A typical remittent fever, lasting for about 2 weeks, was followed by a low-grade elevation of temperature of long duration. The intracutaneous and the agglutination tests were strongly posi-

tive. The lymph glands underwent complete regression after a period of several weeks. In one case, however, the lymph glands suppurated and necessitated incision and drainage (compare Fig. 2.)

Pronounced leukocytosis was found in this case. Neither severe toxic symptoms nor involvement of central nervous system were observed.

The typhoid form was observed in only one case, a 17-year-old girl. Her course was typical and was characterized by a remittent fever of 3 weeks' duration, enlarged spleen, stupor during the first weeks of the disease, leukopenia with lymphocytosis and absence of eosinophils in the blood. No primary focus and no enlargement of lymph glands were found. The intracutaneous test with tularin was positive

on the 6th day of the disease, and the tularemic agglutination test was positive in titer of 1:400 on the 21st day. This patient made good recovery.

THE ULCERO-GLANDULAR FORM was the most common and was characterized (apart from its usual features) by the central nervous system involvement and by the unusual location of the primary focus.

*a. Involvement of the central nervous system* was the most striking feature of this epidemic. It consisted mostly of early involvement of the meninges. This was observed in almost one-half of the hospitalized cases (28 out of 58). All these cases showed either signs of meningism or serous meningitis, and some of them in addition had signs of cerebral involvement in form of men-

Table 3

Location of the primary focus in 115 cases of ulcero-glandular form of tularemia during the epidemic outbreak in settlements of Asino and Jaja.

Location of the primary tularemia focus	Number of cases	Percentage
A. Lower extremity	81	70.4
a. foot	15	
b. leg	63	
c. thigh	3	
B. Upper extremity	18	15.7
a. hand	7	
b. forearm	5	
c. elbow	5	
d. arm	1	
C. Neck or face	16	13.9
a. supraclavicular or suprascapular region	3	
b. neck	7	
c. cheek	3	
d. chin	1	
e. nose	2	
Total	115	100.0

ingo-encephalitis. These rare observations are being reported in a separate paper<sup>7</sup>. The signs of the meningism or serous meningitis were usually transient, so that only one fatality was observed among these cases.

*b. The primary focus* was in each case of the ulcero-glandular type of tularemia in the form of a typical papule, later pustule, surrounded by an area of infiltration. Later a small oozing ulceration remained, which, in the absence of secondary infection, gradually dried and became covered with a scab. The surrounding infiltration in half of the cases disappeared after 1 to 2 weeks. In another half of the cases it lasted 2, 3 and 4 weeks before it underwent resolution. Regional lymphangitis was not seen among our cases. In 3 of the cases secondary small pustules developed around the primary foci and disappeared after a few days.

The location of the primary focus in the 115 cases of ulcero-glandular type of tularemia is given in Table 3.

The location of the primary focus in this epidemic is atypical and is not found in such extent in any other publication about tularemia, except in

Olin's<sup>17</sup> cases. Nor in Soviet Russia has this type of epidemic been reported previously. This is evident, if one compares the location of the primary focus in our cases and in those reported by Russian authors (Table 4).

Figure 3 shows the primary focus on the neck, and a regional lymphadenopathy. Figure 4 shows a typical primary focus in form of a pustule on the lower part of the leg.

*c. General constitutional symptoms*, as described in the classical accounts of Francis<sup>6</sup> and his followers, were found in all early hospitalized cases of the ulcero-glandular form of tularemia. These were: acute onset of the disease with chills, prostration, toxic symptoms, severe headache and high fever.

*The fever* was remittent in a typical way. 40% of the cases had high fever type: 4 to 10 days of high fever up to 40°C, followed by several weeks of low-grade elevation of temperature. Another 40% of the cases had moderate fever: 3 to 7 days of fever up to 38 to 39°C, followed by 1 to 3 weeks of low-grade elevation of temperature. The remaining 20% of cases had recrudescent fever: 3 to 7 days of fever

Table 4

Frequency of the involvement of the lower extremity in the ulcero-glandular form of tularemia in Soviet Russia (according to Pokrowsknajazi) as compared with the epidemic in Asino and Jaja.

Author	Place of the epidemic	Total Number of cases of ulcero-glandular form of tularemia	Number and percentage of cases showing the primary focus on the lower extremity.	
			Number	Percentage
L.M. Chatenewer	Gintma	164	7	4.3
L.M. Chatenewer	River Bialka	40	2	5.0
D.A. Golov	Ural	102	15	14.7
G.J. Sinaj	Kazakhstan	32	4	12.5
	Total	338	28	7.2
G.B. Jerzy Glass	Asino and Jaja, Novosibirsk Province, Siberia	121	81	66.9

up to 38 to 39°C, followed after a short period of low-grade elevation of temperature and another recrudescence of fever up to 38 to 40°C, usually occurring on the 10th to 14th day of the disease. This recrudescence lasted for 2 to 6 days and was followed by another period of low-grade elevation of temperature.

No relation was found between the site of the primary focus and the type of fever. In most cases of tularemia involving the central nervous system usually high fever type was present.

*d. Regional lymphadenitis* was found in all 115 cases of the ulcero-glandular form of tularemia. The location of the lymphadenitis was listed in Table 2, which shows its distribution according to the anatomical features of the lymphatic drainage. The lymph glands were very painful at the beginning, but gradually underwent regression, in 3 to 6 weeks. In many instances the enlargement of lymph glands persisted for several months. Fig. 5 shows a typ-

ical picture of the enlargement of femoral lymph glands, which was found in two thirds of our cases.

Only in 9 out of 58 hospitalized tularemia cases did suppuration of the lymph glands necessitate surgical intervention (incision and drainage).

*e. Blood picture.* Red blood cells and hemoglobin showed in general no characteristic changes, although a slight microcytic hypochromic anemia was noted in many of the prolonged cases.

The white blood cell count at the beginning of the disease was almost constantly normal. In 29 of 35 cases, which were examined in the first week of the disease, the white blood cell count ranged between 3000 and 6000 cells per cmm. This was the normal range of white blood cell count in the population of settlements and adjacent villages of Siberia at that time, due probably to nutritional deficiency and malnutrition. The white blood cell count was increased above 7000 in only 7 cases, so that the average value of

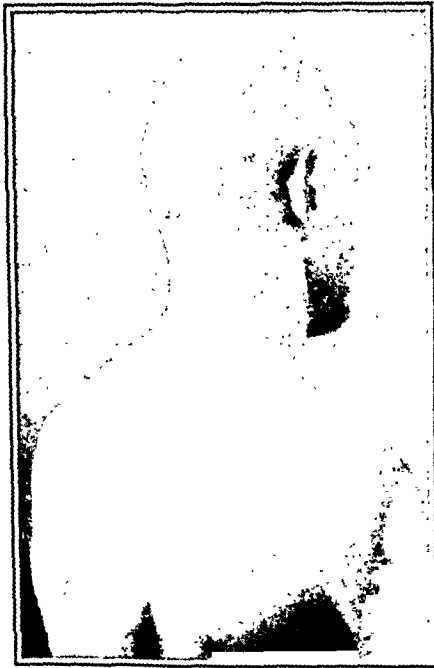


FIG. 3

FIG. 3. Ulcero-glandular form of tularemia, with primary focus located on the neck and regional lymphadenopathy.



FIG. 4

FIG. 4. Primary focus located on the leg in a case of ulcero-glandular form of tularemia.

white blood cells in the first week of tularemia was 5600 per cmm. (average value of 36 cases).

Leukocytosis, which was described as a characteristic feature of tularemia, was found in our cases only in the 2nd or 3rd week of the disease, or later. In 11 out of 17 cases, examined at this time, leukocytosis was found, with values between 7000 and 28000 per cmm. The average of 17 cases was 10200 per cmm.

The differential count of white blood cells in our cases showed the following deviations of the normal: (1) Absence of eosinophils; this was found in the 1st week of the disease in 28 out of 35 (80%) and in the 2nd and 3rd weeks in 60% of cases. (2) Shift to the left; an increase in amount of immature cells above 5% was found in the 1st week of the disease in 32 out of 35 (91%), with an average value of 12%. In the

2nd or 3rd weeks of the disease the shift to the left was found in 14 out of 17 (80%), with an average value of immature of 7%. (3) Monocytosis; this was found in approximately half of our cases (in 18 of 35), with an average value of monocytes of 8% in the 1st week of the disease. (4) Lymphocytosis; this was found very often. In some cases it seemed to depend on the youth of the patient. On the other hand lymphocytosis was observed also in 12 adults.

*f. Sedimentation rate* was examined in 39 cases of tularemia. The micro-method of Panchenko was used. In the 1st week the sedimentation was accelerated in all 20 examined cases. Values between 13 and 44 mm. in the 1st hour were found, with an average of 25 mm. (normal values for this method range between 2 and 8 mm.). In the 2nd, 3rd, and 4th weeks of the disease the



FIG. 5. Femoral lymphadenopathy in a case of ulceroglandular form of tularemia, with primary focus on the leg.

sedimentation rate was increased in 16 out of 19 cases, with values between 14 and 62 mm. averaging 28 mm. after the 1st hour. The highest values of sedimentation were found in cases of tularemia complicated by suppuration of regional lymph glands.

*g. Complications.* The strain of *Bacillus tularensis* which was the cause of this epidemic showed definite neurotropic affinity. This is suggested by the frequent involvement of the central nervous system and by the almost complete absence of any other complications. None of the 121 cases showed pulmonary involvement. Cutaneous complications consisted only in a multi-form erythema observed in 1 case and in a transient maculo-papulous exanthem observed in 2 other cases during the 3rd and 4th weeks of the disease. The renal involvement was seen in only one case, in which a previous glomerulo-nephritis was aggravated under the influence of the tularemia and resulted in uremia and death.

*Treatment:* Immune serum was not available for the treatment of these cases. Streptomycin was not yet known at that time (1941). Only symptomatic care could be offered. In spite of this inadequate regimen, 119 out of 121 cases recovered after a more or less prolonged course lasting up to several months.

*The mortality rate* was very low (1.7%) and corresponds to the rate observed in Soviet Russia. Only 2 fatalities occurred in 121 cases: one due to the exacerbation of a previous glomerulo-nephritis, resulting in uremia, another due to severe meningo-encephalitis.

*Summary.* One hundred and twenty-one cases of tularemia resulting in 2

deaths were observed during a short epidemic outbreak in settlements of deportation Asino and Jaja, Novosibirsk Province, Siberia, Soviet Russia, during the Summer of 1941. One hundred and fourteen cases were confirmed by serologic and, or, intracutaneous allergic tests, and 115 out of 121 belonged to the ulcero-glandular form of this disease.

Since no direct contact of infected persons with rodents could be traced and the primary tularemic focus was located in two-thirds of all cases on the leg or on the foot, the epidemic must have been transmitted by insects, probably mosquitoes. The source of infection was the water-rats populating the shores of the Czulym river at the time of infection.

The morbidity rate was tremendous in the settlement of Jaja, where 52 cases out of the entire population of 460 contracted tularemia, a morbidity rate of 11.3%. In the other settlement of Asino the morbidity rate was smaller, and averaged only 1.8% (33 cases of tularemia out of the population of 1840).

Another striking feature of this epidemic was an early and transient involvement of the central nervous system, consisting of signs of meningism, serous meningitis and at times meningo-encephalitis. Almost half of the early hospitalized cases of tularemia (28 out of 58) showed an unusual characteristic tetrad: (1) meningism or serous meningitis, (2) high fever, (3) primary tularemic focus in form of a small papule or pustule on the leg or foot, and (4) regional femoral or inguinal lymph gland swelling.

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# PRINCIPLES IN THE MANAGEMENT OF CHRONIC NON-SPECIFIC ULCERATIVE COLITIS\*

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THE treatment of chronic non-specific ulcerative colitis is as poorly defined as is its etiology. Each theory as to its cause has led to a corresponding form of therapy. In turn, the good results that have followed each therapeutic procedure, irrespective of the other measures employed, have been interpreted as support for a particular causation. That accounts for the varying emphasis, both in etiology and treatment, on infectious, allergic, metabolic and psychogenic factors. In the more severe cases, however, without reference to the cause and largely because of its frequent good immediate results, ileostomy is commonly advocated.

None of these therapeutic procedures, however, or any combination of them often brings about a permanent cure. The relief that follows, no matter how complete, is usually of a temporary nature. In a review of the recent literature, covering 3639 medically treated cases followed from 1 to 10 years, including 148 of our own, only 8% obtained relief for an extended period, while 46% were admittedly unimproved and 5% died without operation (Chart 1). The remaining 41% showed some signs of improvement, but most of them remained more or less incapacitated and often developed a recurrence of activity. Of the unimproved cases 638 had an ileostomy.

Thirty-four per cent of these died, often no doubt because of delay in resorting to surgery, and another 32% secured no significant relief. Of 184 finally subjected to a colectomy and followed, 27% died, while 54% may be regarded as cured; of the remaining 19%, improved or unimproved, it is probable that many had only a partial colectomy.

Were it not for the ileostomy stoma, with which the colectomized patients are left and which in most instances is permanent, this operation would seem to be an ideal therapeutic procedure. Furthermore, if done earlier in the course of the disease, before the general condition of the patient is markedly impaired, the mortality from this operation probably would be trivial. At present, however, colectomy necessarily is reserved for the otherwise hopeless cases. Even so, both Cattell<sup>3</sup> and Cave<sup>4</sup> have reported on ten year experiences with only a 10% mortality.

Preliminary to every colectomy, however, an ileostomy is necessary. The mortality from this procedure is higher because most clinicians agree to it only when the patient's condition is at its worst: when, in spite of temporary supportive measures, he is emaciated, chemically disorganized, more or less anemic and highly toxic. In the two-thirds that nevertheless survive the ileostomy, the condition of the patient

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usually improves: his appetite returns, the chemical disturbances are corrected, the diarrhea subsides, the ulcers heal and he gains weight. Although the improvement may not be permanent, due in many instances to complications and in others apparently to the natural course of the disease, one wonders by what means the ileostomy so often brings about a subsidence of the

cases reported a year ago, to secure results comparable to those obtained by surgical ileostomy. It seems probable, therefore, that at least one of the factors in the beneficial effects of a surgical ileostomy lies in withholding from the colon the small intestinal contents. This does not imply that the small bowel contents are abnormal, though they may be; only that, under the con-

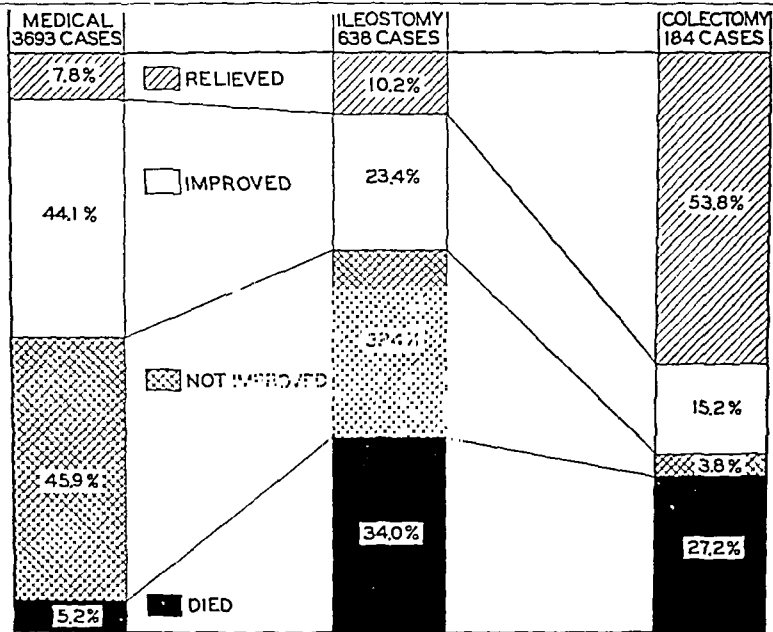


FIG. 1.—Results from therapy in chronic ulcerative colitis patients.

immediate disturbances.

With the idea of determining whether or not the relief is due merely to the diversion of the intestinal current, Machella<sup>6</sup> tried out a less hazardous procedure, a so-called “medical ileostomy”: intubating the intestine to a point just short of the disease process and withdrawing by constant suction the residual material. By such a technique, combined with a high protein and high calory diet but uncomplicated by the use of antibiotics or other medicaments, he was able, in a series of 12

ditions of the disease, they are disturbing to the colon.

A careful study of small intestinal functions and its contents in patients with ulcerative colitis has not been made, but data are available to indicate an impairment in the absorption of protein products (Zetzel, Banks and Sagall<sup>9</sup>; Elsom, Dickey and Chornock<sup>5</sup>; Benson, Brown and Seldon<sup>2</sup>). Also in some instances we, as well as others, have found, on roentgenological investigation, an intestinal hypermotility. Furthermore, although we did

not appreciate its significance at the time and few actual measurements were made, we noted repeatedly that for the first few days after introducing an ileal tube a large amount of contents was aspirated, whereas later, when the patient's condition had improved, the amount was markedly reduced. Thus not only is the absorption of food material impaired in active ulcerative colitis, but the small bowel contents enter the cecum in excessive quantity.

Under normal conditions an increased ejection of intestinal contents into the cecum follows the ingestion of food and this is regarded as a factor in initiating mass movements in the colon. We may assume, therefore, that the excessive amount ejected in ulcerative colitis causes an increased irritability and contractility of the colon in that disease. Thus it would seem that we have a rational basis for the diversion of small intestinal contents from the colon, our first principle in the treatment of ulcerative colitis. At any rate we have an empirical basis, in that after both surgical and medical ileostomy the condition of the patient improves.

The second principle that we wish to emphasize, and a more important one, is the employment of a nutritionally adequate and easily absorbable dietary. In our experience to date this has consisted in the main of an enzymatic protein hydrolysate and dextrimaltose mixture<sup>\*</sup> with added vitamins. This preparation was chosen because the amino acids, like the sugar, require no digestion and are readily absorbed; because quantities in excess of ordinary requirements are easily administered, and because, since it is a thin solution, such residue as reaches the terminal ileum is readily withdrawn. In spite of some loss of the mixture incident to its rapid transit through the

bowel and its consequent aspiration during the first few days, the amount absorbed steadily increases and soon the residue contains no sugar or amino acids. Thus very quickly, as also is indicated by the improved nutrition and morale of the patient, the body's needs are met or exceeded. As further evidence of this in our series, the appetite returned, fever, when present, subsided, demonstrable ulcers healed, diarrhea lessened and the weight steadily increased. After 1 to 2 weeks it frequently was possible to add other food substances and remove the tube.

In view of the results from this program of rest to the colon and an effective diet, we have been encouraged during the past year to try out a series of 12 moderately severe, some quite severe, cases on such a dietary regimen alone. In 24 cases, 12 with and 12 without the tube, all observed within a 2-year period, we have secured satisfactory temporary results in all but 2: one of these, obviously allergic, showed some improvement but relapsed as soon as other foods were added; the other was not cooperative, and died. Four others have had mild relapses, all on an emotional basis, but quickly recovered; all are now gainfully employed. Thus it seems possible that the really essential therapeutic procedure for the immediate control of an attack, is that of securing the absorption of a high protein, high calory diet. In the more severe cases, however, because of the excessive irritation of the colon, this may be impossible unless for a time the colon is put at rest by one of the ileostomy procedures.

In spite of our emphasis on these 2 principles in management we do not wish to be understood to disregard procedures designed to combat emotional and infectious factors, or to overlook, in the presence of clear indica-

<sup>\*</sup> Laboratory Product No. 197, consisting of 50% Protolysate and 50% dextri-maltose, generously supplied by Mead Johnson and Company.

tions, the ordinary measures for the control of anemia, allergic manifestations and blood electrolyte depletion.

The significance of emotional factors in the development of ulcerative colitis and its relapses is now well established. All observant clinicians are aware of this. Two thirds of Sullivan's<sup>7</sup> cases and one half of our total series of 157 showed some evidence of an unstable personality or of emotional crises preceding the onset of the disease. Almy and Tulin's<sup>1</sup> as well as White and Jones's<sup>8</sup> observations of the lower bowel through the sigmoidoscope indicate that the large intestine contracts when the subject is under emotional stress. This may be a purely reflex nervous phenomenon or it may be the result of an increase in the amount of small intestinal material injected into the cecum, such as is known to occur from excitement as it does after the ingestion of food.

At any rate coincident therapy directed toward the prevention, control and elimination of emotional factors is clearly indicated in all cases. This we have included in the management of all our patients, often seeking the help of the psychiatrists. Its share in the favorable results obtained is difficult to determine, but we suspect that it has been of great assistance and that it accounts to some extent for the good results reported after various other types of therapy.

Likewise infection undoubtedly is an important factor in the total picture of non-specific ulcerative colitis. It is inconceivable that this should not be so, since the feces consists in large part of microorganisms and the mucosal surface of the colon is not intact. Infection surely accounts for certain features of the disease, especially some of its complications, but it has not been demonstrated that any particular organism is the primary etiologic agent. In any event, when the patient

is febrile or shows other systemic signs of infection, the antibiotics and chemotherapeutic agents are indicated. Furthermore, since their administration orally and per rectum has seemed effective in the hands of some clinicians, we venture the suggestion that their action might be enhanced if they were administered through a tube directly into the lower ileum or cecum, thus reaching the affected area in more concentrated form. Their general effect, in our experience, however, has not radically altered the primary bowel lesion, and without them, in the uncomplicated cases, we have secured equally satisfactory results.

**Summary and Conclusions.** Thus we have presented briefly certain so-called principles, especially rest to the colon and superalimentation, for the treatment of chronic non-specific ulcerative colitis. In advocating intubation as a means of bringing about colon rest, we fully appreciate its difficulties, its strain on the subject and the time, skill and patience required of the physician, but at least its limited employment in our hands has seemed to demonstrate one of the factors that tends to prolong and aggravate the disease. Fortunately, as a practical procedure, it is not usually required if a fully adequate and easily absorbable diet is administered. Such a dietary regimen is not original with us, but our experience has served to emphasize its maximal importance and its practicality. At the same time we have approved the employment of all measures calculated to allay or remove emotional disturbances, to control infection and to overcome anemia, allergic reactions and abnormalities in the chemical constituents of the blood.

Until its specific etiology is established, be that a bacterium, a virus, some metabolic fault or some other factor, a cure for chronic non-specific ulcerative colitis, aside from colectomy,

seems improbable. Otherwise the most that can be hoped for is relief of the immediate attack. If this can be obtained by measures other than surgical ileostomy, fewer patients will die and fewer of those who survive will be burdened permanently with an ileostomy stoma.

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# HEATING OF HUMAN TISSUES BY MICRO WAVE RADIATION\*

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DUE to a slow rate of penetration, the heat furnished by most clinical methods of heat therapy is relatively ineffective in raising deep tissue temperatures. Short wave diathermy, the only available procedure for deep and rapid heating, also induces generalized effects and is, therefore, not easily adapted to the heating of localized masses of tissues. Since deep heating is only successfully accomplished through the medium of high frequency electrical energy, numerous attempts have been made to apply for therapeutic purposes the very high frequencies near the infra red region of the spectrum. Hemmingway and Strenstom<sup>6</sup> have discussed the possibility that deep and local heating could be accomplished by utilizing the optical properties of these short wave lengths. Krusen *et al.*<sup>7</sup> have described a commercial instrument and analyzed the physical properties of the electrical energy produced in radar systems. The results of their dog experiments indicate that these waves would provide a useful clinical tool. In this respect several investigators<sup>1,5,8</sup> have reported results which suggested that no deleterious effects are induced in personnel exposed to radar radiation.

**Methods.** All 9 subjects were healthy, vigorous individuals. Two males were in their

twenties, another 2 in their thirties, and the remaining 2 in their sixties. Of the females, 2 were in their twenties and the third in her forties.

The experimental procedure briefly was as follows: Each subject rested quietly for about 1 hour in a room with a temperature of approximately 23° C. Control observations were made during the succeeding 15 minutes and then thermocouples were removed from the thigh area to be treated. Immediately after a 15 or 30 minute period of exposure in the radiation field of a microwave generator (the magnetron tube oscillated at a frequency of 2450 megacycles per second—wave length 12.2 cm.), the thermocouples were replaced and the cooling of the tissues observed for periods of 30 to 130 minutes. The thermocouples were of copper-constantan and a type K, Leeds & Northrup potentiometer was used to measure the emf developed. Five surface thermocouples were placed on the area treated and 4 additional couples were placed at lower levels of the same leg and at corresponding points of the other leg. In a number of experiments additional thermocouples were distributed over the body, particularly on fingers and toes. To measure deep and superficial tissue temperature, hypodermic needles were inserted in the thigh, thermocouples threaded through them and the needles withdrawn, leaving the couples in place. Calibrated clinical thermometers were used to obtain rectal temperatures.

Microwave energy was directed by a 4-inch hemisphere (A), a 6-inch hemisphere (B), or a 4-inch corner or angle director (C) placed at a distance of 5 cm. from the thigh surface. Power outputs were 25, 50 or 80 watts; of the 17 experiments employing the 6-inch director, 3 were with 25 watts, 11

\* Aided by a Grant from the National Foundation for Infantile Paralysis.

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with 50 watts and 3 with 80 watts. The remaining 6 experiments were equally divided among A and C directors at 50 watts. The preponderance of 50 watt exposures was related to employment of this dosage in current clinical trials of the efficacy of this mode of therapy.

**Results.** The temperature gradient from the surface of the thigh to a depth of 56 mm. is presented in Table 1. The consistent break in the temperature gradient at both 3 and 30 mm. was indicative of the presence of fascial planes at these levels. From 30 to 56 mm. the temperature appears to

though a normal gradient pattern was observed from these depths to the skin, it was at a much higher absolute temperature. The heat content of the outermost 25 mm. of tissue was still high and heat losses were occurring from this mass.

The maximum temperatures observed at 3 depths of the thigh, surface (0 mm.), subcutaneous (4-15 mm.), and muscle (over 30 mm.) following the heating of the tissue, are shown in Table 2. Due to the properties of micro wave radiation it is impossible to measure temperature changes during the

TABLE 1. — TEMPERATURE GRADIENTS IN THE TISSUES OF THE LATERAL ASPECT OF THE THIGH

Depth mm.	Pre-treatment ° C.	Post-treatment <sup>a</sup> ° C.
0	31.4	33.3
3	30.7	32.7
6	31.6	33.4
9	32.5	33.9
13	32.4	34.7
16	33.8	35.0
19	33.5	35.3
22	34.6	35.7
25	34.6	36.0
28	35.5	35.4
31	35.0	36.0
34	35.9	35.9
37	35.7	36.2
41	36.1	36.2
47	35.9	36.2
56	36.1	---

<sup>a</sup>Obtained at cessation of experiment (mean time, 57 minutes) when deep muscle temperatures had returned to control levels.

be at a constant level with only minor fluctuations. The general pattern of the gradient in the control observations is in essential agreement with results reported by Bazett and McGlone<sup>2</sup> and Barcroft and Edholm,<sup>1</sup> although the actual values are different. These discrepancies are undoubtedly related to the great variability observed in deep temperatures in different muscles and at different horizontal levels of the same muscle. These factors have been discussed in detail by Buchthal *et al.*<sup>3</sup> The second set of gradients was obtained during the cooling period at the time when deep muscle temperatures (30 mm. plus) were essentially at control levels. Al-

though a normal gradient pattern was observed from these depths to the skin, it was at a much higher absolute temperature. The heat content of the outermost 25 mm. of tissue was still high and heat losses were occurring from this mass. The maximum temperatures observed at 3 depths of the thigh, surface (0 mm.), subcutaneous (4-15 mm.), and muscle (over 30 mm.) following the heating of the tissue, are shown in Table 2. Due to the properties of micro wave radiation it is impossible to measure temperature changes during the period of heating and, therefore, the maximal temperature must be arbitrarily presented as an indication of the change in tissue temperature. The rise in surface temperature was roughly equivalent with the B director at 3 generator outputs. This 3 to 5°C. increase correlated with the subjective evaluation of a mild and pleasant heating volunteered by patients and subjects. Erythema was observed in only a few instances and this with other directors and higher powers. The alterations in the subcutaneous temperatures were most striking with both A and B directors. In the majority of instances these values were higher than simultaneously determined muscle tem-

The elevation of deep tissue temperatures induced by micro wave radiation was maintained for at least 30 minutes and up to 2 hours (Figures 1 to 5). On some occasions the temperature at the subcutaneous level was not increased so greatly as the muscular tissue (Figure 2). In this subject the subcutaneous thermocouple was rather shallow (4 mm.). As was to be expected, surface temperatures remained elevated for were obtained.

TABLE 2. — ALTERATIONS IN TISSUE TEMPERATURES OF THE LATERAL THIGH WITH APPLICATION OF MICRO WAVE RADIATION (12 CM.) FOR 15 MINUTES

	"B" Director		"B" Director		"B" Director		"B" Director		"C" Director	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Surface Temp.	32.4	31.7-33.1	34.8	34.4-36.4	39.1	31.3-38.9	36.4	36.0-36.8	35.6	30.1-31.6
Maximal	35.6	35.2-36.6	38.5	37.3-39.8	42.9	41.8-43.9	40.6	39.3-41.9	38.1	37.2-39.0
Δ	3.2		3.6		10.7		4.0		2.5	
Subcut. Temp.	32.5	32.0-33.0	36.1	35.1-37.3	35.3	35.2-35.3	35.3	35.2-35.3	35.0	34.8-35.3
Maximal	38.1	37.9-38.2	38.5	37.3-39.8	39.3	38.9-39.9	39.3	38.9-39.9	38.1	37.2-39.0
Δ	5.6		2.4		4.0		4.0		3.1	
Muscle Temp.	35.3	34.4-36.1	36.1	35.1-37.3	35.3	35.2-35.3	35.3	35.2-35.3	35.0	34.8-35.3
Initial	36.6	36.3-36.8	36.1	35.1-37.3	35.3	35.2-35.3	35.3	35.2-35.3	35.0	34.8-35.3
Maximal	36.6	36.3-36.8	36.1	35.1-37.3	35.3	35.2-35.3	35.3	35.2-35.3	35.0	34.8-35.3
Δ	1.3		2.4		4.0		4.0		3.1	

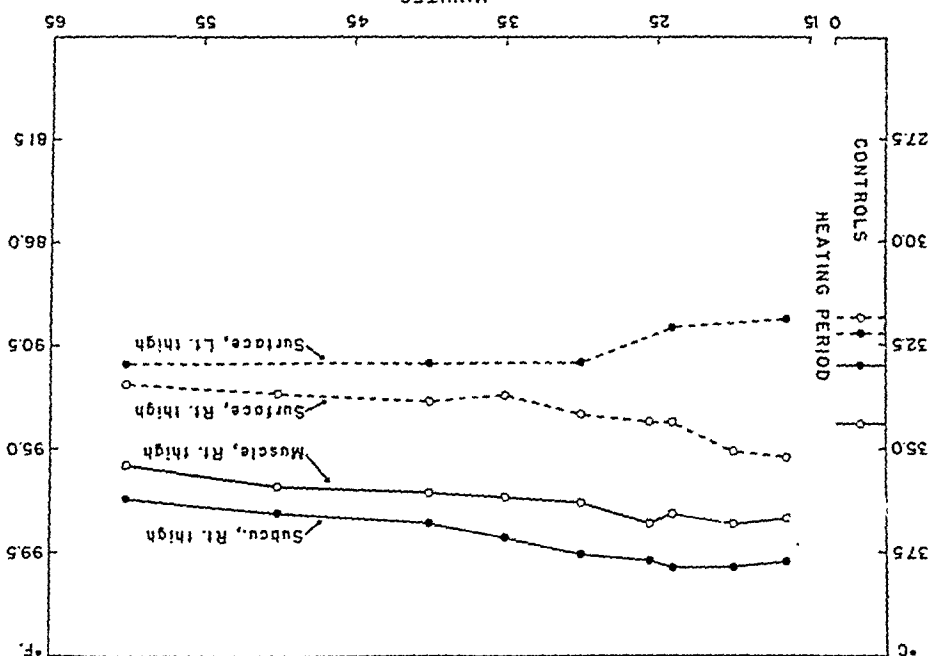
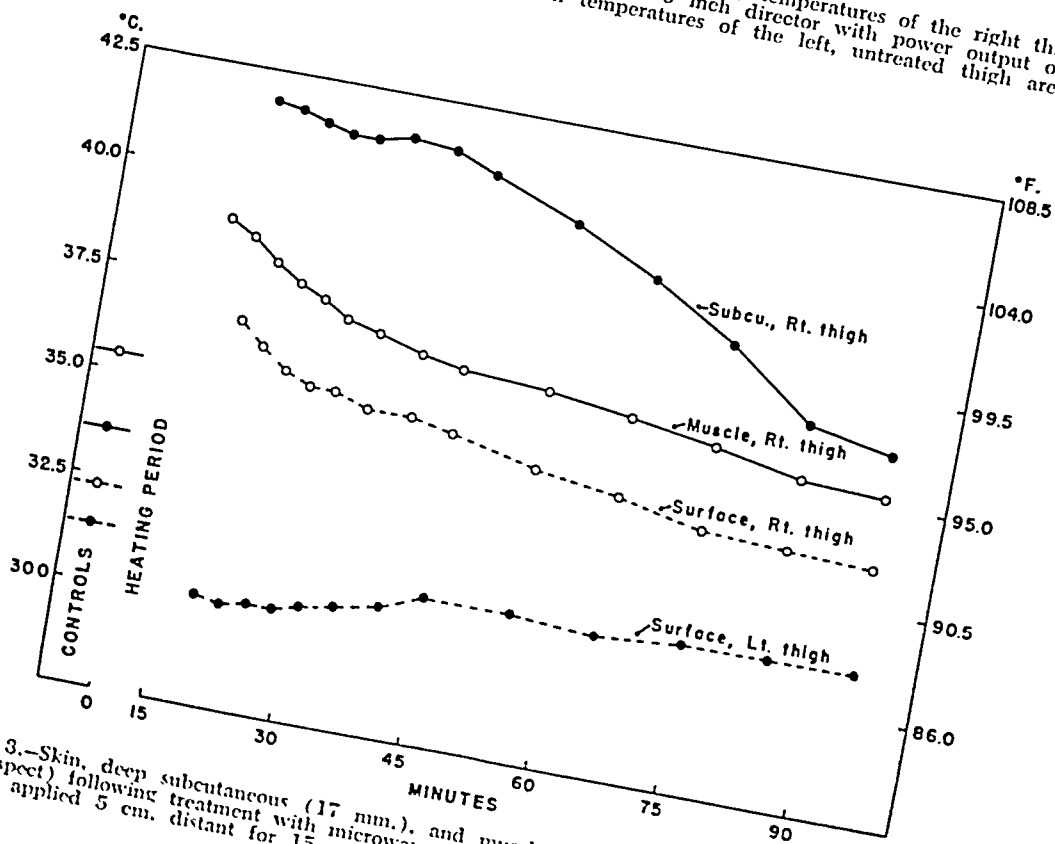
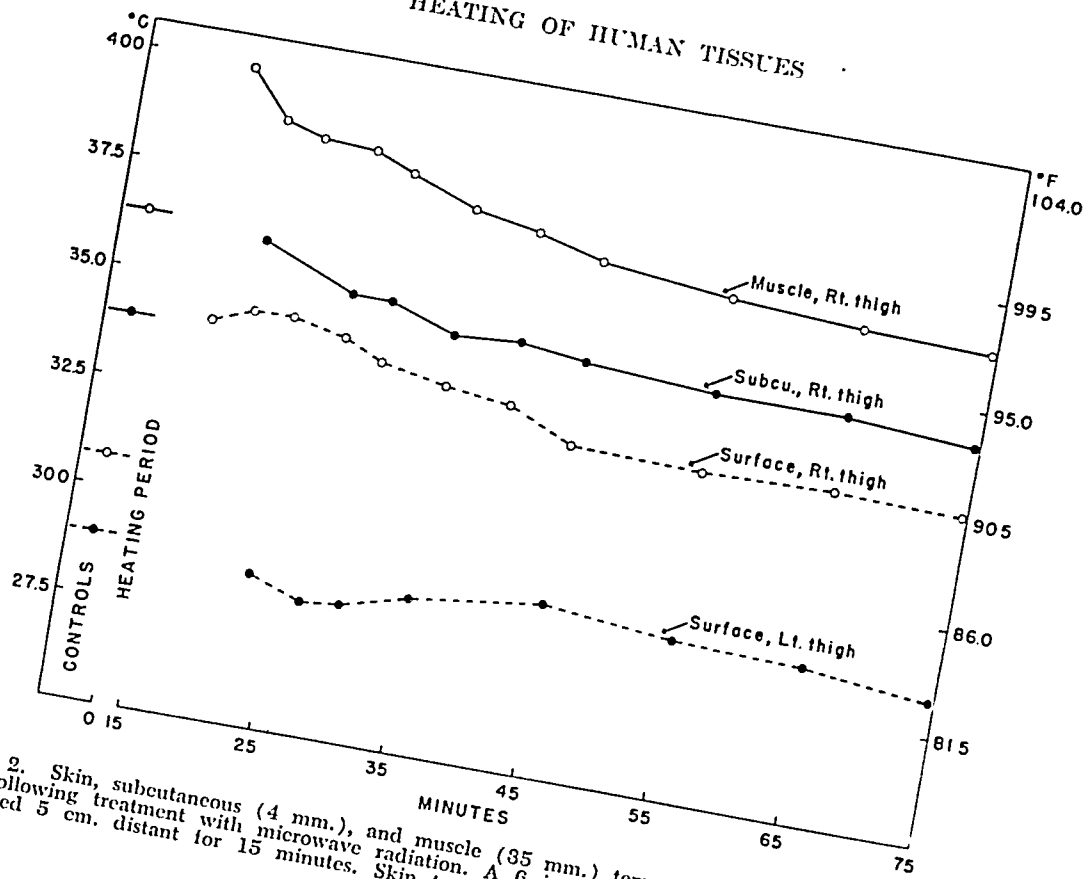


FIG. 1.—Skin, subcutaneous (9 mm.), and muscle (29 mm.) temperatures of the right thigh (lateral aspect) following treatment with microwave radiation. A 6 inch director with power output of 25 watts was applied 5 cm. distant for 15 minutes. Skin temperatures of the left, untreated thigh are also presented.

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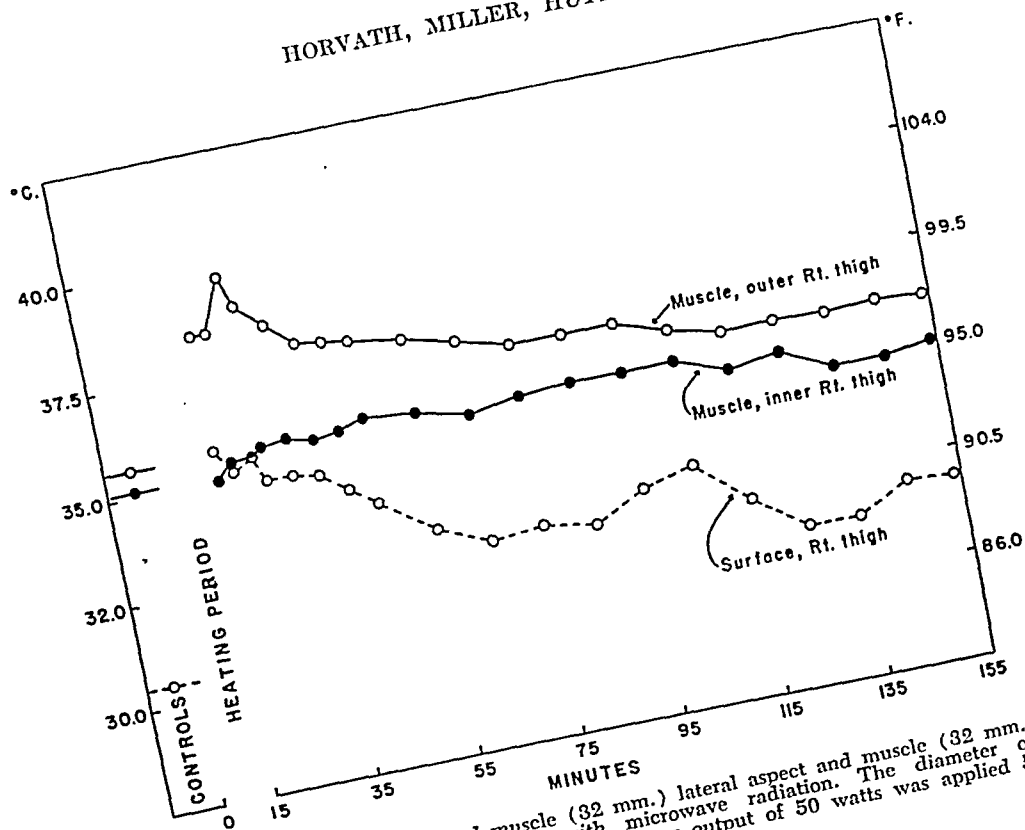


FIG. 4.—The temperatures of skin and muscle (32 mm.) lateral aspect and muscle (32 mm.) medial aspect of the right thigh following treatment with microwave radiation. The diameter of the thigh at these points was 170 mm. A 6 inch director with power output of 50 watts was applied 5 cm. distant for 15 minutes.

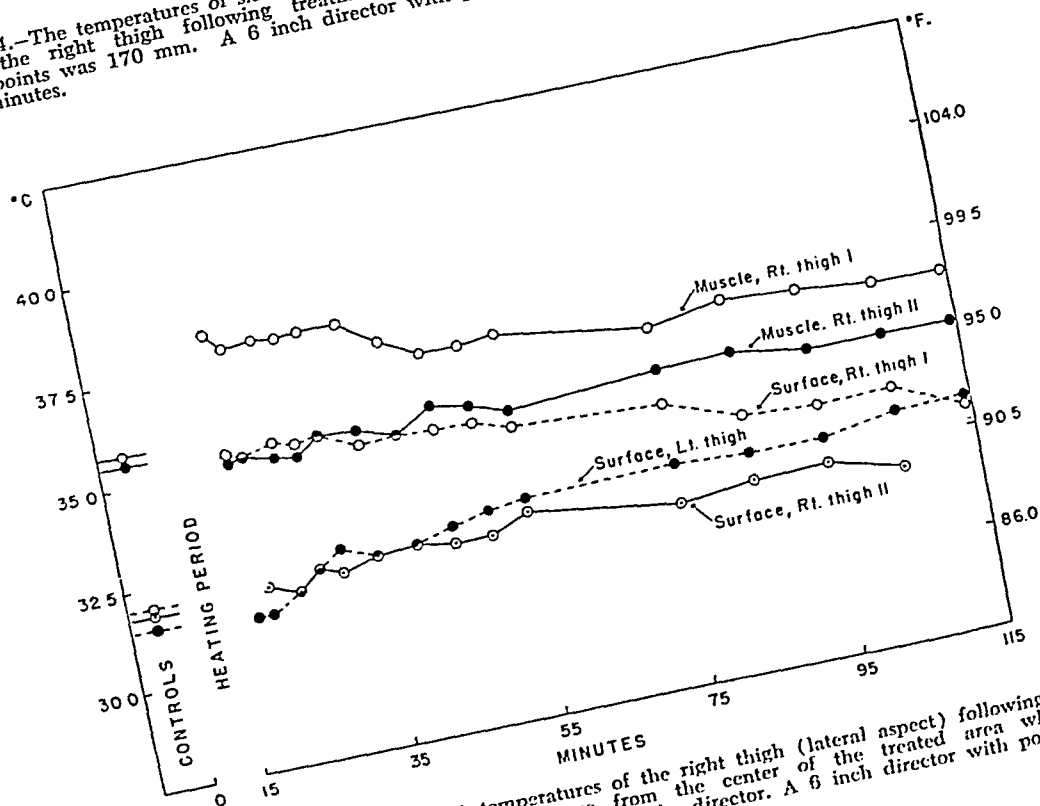


FIG. 5.—Skin and muscle (30 mm.) temperatures of the right thigh (lateral aspect) following treatment with microwave radiation. Number I values are from the center of the treated area while Number II values are 130 mm. lower and outside the area of the director. A 6 inch director with power output of 50 watts was applied 5 cm. distant for 15 minutes.

somewhat longer periods than was the case for the deep. The frequent occurrence of an initial transitory decrease in the surface temperatures of the left thigh may be indicative of a reflex vasoconstriction.

Deep heating was readily accomplished by micro wave radiation. In order to determine the extent of this effect additional experiments were conducted. When thermocouples were inserted at equivalent depths in the muscle tissue of opposite sides of a treated thigh, no positive evidence of heat transfer across the muscle and bone mass was noted (Figure 4). However, the muscle temperature of the inner surface of the thigh did not exhibit the gradual fall in temperature normally observed in resting muscles.<sup>3</sup> Since this phenomenon did not occur, it might be possible to interpret the small rise as indicative of some transfer, but in a repetition of this experiment on another subject this slight change was not duplicated. In Figure 5 a similar experiment is shown with a second thermocouple in the same muscle but 130 mm. lower and at a distance of 64 mm. from the edge of the director. Neither muscle nor surface temperatures at this point were elevated following treatment. In 2 other experiments surface and muscle temperatures were measured at various points within the area of the B director. Temperature determinations were within 0.3 to 1.0°C. Generally lower muscle temperatures were found nearer the periphery. Surface temperatures were not consistently different at any point within the area or during different experiments.

No evidences of generalized effects were observed. Rectal temperatures remained within  $\pm 0.1^\circ\text{F}$ . of control values. Reflex vasodilation, determined by multiple toe and finger temperature measurements, was not induced.

**Discussion.** Exposure of the thigh to the radiation field of a micro

wave generator resulted in definite changes in tissue temperatures. The effects were relatively local in that they were limited to the area of the director employed and did not penetrate to depths much beyond 60 mm. The output of the generator determined to a certain extent the depth of penetration and the site of greatest temperature alteration (Table 2). However, regardless of generator output the greatest changes in temperature were observed in the subcutaneous and contiguous muscle layers. With larger outputs, higher but not the highest temperatures were recorded in deep muscle. Whether this was due to actual penetration of energy to these depths or just to heat transfer was not definitely determined. That the latter may be involved is suggested by the high temperatures observed in the more superficial muscle layers. The normal gradient from subcutaneous to muscle tissue was reversed in practically all instances.

Osborne and Frederick<sup>9</sup> have reported the only other data on human subjects. They found a mean temperature of  $40.1^\circ\text{C}$ . at a depth of approximately 50 mm. Unfortunately, they failed to mention the power output of their generator. It was quite likely at least 80 watts. If such was the case, there would be essential agreement with the findings reported herein. A complete comparison of the effects of micro wave radiation on heating of tissues is not possible since Osborne and Frederick have presented only figures for one depth. Data presented by Krusen *et al.*<sup>7</sup> on dogs is essentially in agreement with the results on human tissue, if depth and not histological distinctions are employed for comparison. In both species the maximum elevations of temperature are observed at depths of approximately 20 to 35 mm. At other levels the effects are of a smaller order of magnitude.

The slight elevations of skin temperature observed (Table 2) are interesting in that subjectively patients report only a sense of pleasant warmth and are not conscious of the higher internal temperatures. Furthermore, erythema is noted in a very small percentage of cases and has been observed most frequently in those patients who have been perspiring prior to or during the early phases of the treatment. In one respect this illusion of mild warmth is dangerous, since many individuals, both patients and operators, believe that only a small amount of heat is being given and are tempted to increase the power output with possible ill effects in the deep tissues. This danger is especially likely to occur to those who are accustomed to short wave diathermy where skin sensation is the determining factor in dosage.

The cooling curves obtained are not susceptible to easy analysis since two distinct slopes were generally evident—an initial period of short duration with a rapid fall and a succeeding prolonged period during which the temperatures dropped at a much slower rate. These prolonged cooling curves offer opportunity for speculation regarding the influence of this mode of heating on the rate of blood flow through the heated tissue. Krusen *et al.*<sup>7</sup> have reported striking increases in venous flow in the dog's hind limb during and following treatment. However,

rough calculations based on a mean temperature rise of 5°C. in human tissues indicated that cooling should have occurred within 15 to 30 minutes even with no increase in blood flow. But the cooling curves were much more prolonged, suggesting either no change or a small increase in the blood flow through the heated tissues. Information on this aspect is now being obtained.

**Summary.** The employment of high frequency electrical energy in the 12 centimeter band (2450 megacycles per second) of the electromagnetic spectrum provided a means of selectively heating local masses of tissue. The magnitude and depth of heating can be modified by varying directors and the power output of the generator. Maximal temperatures observed following a 15 minute period of heating, utilizing a power output of 50 watts and a 6-inch director, were 36.4°C. at the surface, 44°C. at subcutaneous levels, and 40°C. in muscle tissue. In the majority of the experiments the temperature gradient from subcutaneous tissue or muscle to surface was not modified greatly as a consequence of this mode of heating. However, in a large number of instances the subcutaneous to muscle gradient was reversed. High internal temperatures were secured with only incidental elevation of surface temperatures. No increases in rectal temperature were observed.

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CLINICAL EVALUATION OF PHENINDAMINE  
(2-METHYL-9-PHENYL-2,3,4,9-TETRAHYDRO-1-PYRIDINDENE  
HYDROGEN TARTRATE) AS AN ANTIHISTAMINIC AGENT

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AN antihistamine substance may be defined as one "capable of diminishing or preventing several of the pharmacological effects of histamine"<sup>1</sup> by competing with it for a particular site of action or for the same tissue receptor, rather than by the production of diametrically opposite pharmacological responses. "This type of antagonism is reversible and one of the most specific in nature".<sup>4</sup>

Despite its specificity, it has been repeatedly shown that the reaction does not necessarily involve closely related chemical analogues but may be produced by a diversity of compounds, which, while sharing an antihistamine action in common, vary considerably in their pharmacological activity. For instance, certain of the benzhydryl alkamine ethers, to which class Benadryl belongs, show, in addition to their antihistaminic activity, an atropine-like action, not shared by equally potent antihistamine substances such as anter-

gan, and closely related alpha-amino-pyridine derivatives, of which Pyribenzamine is one.

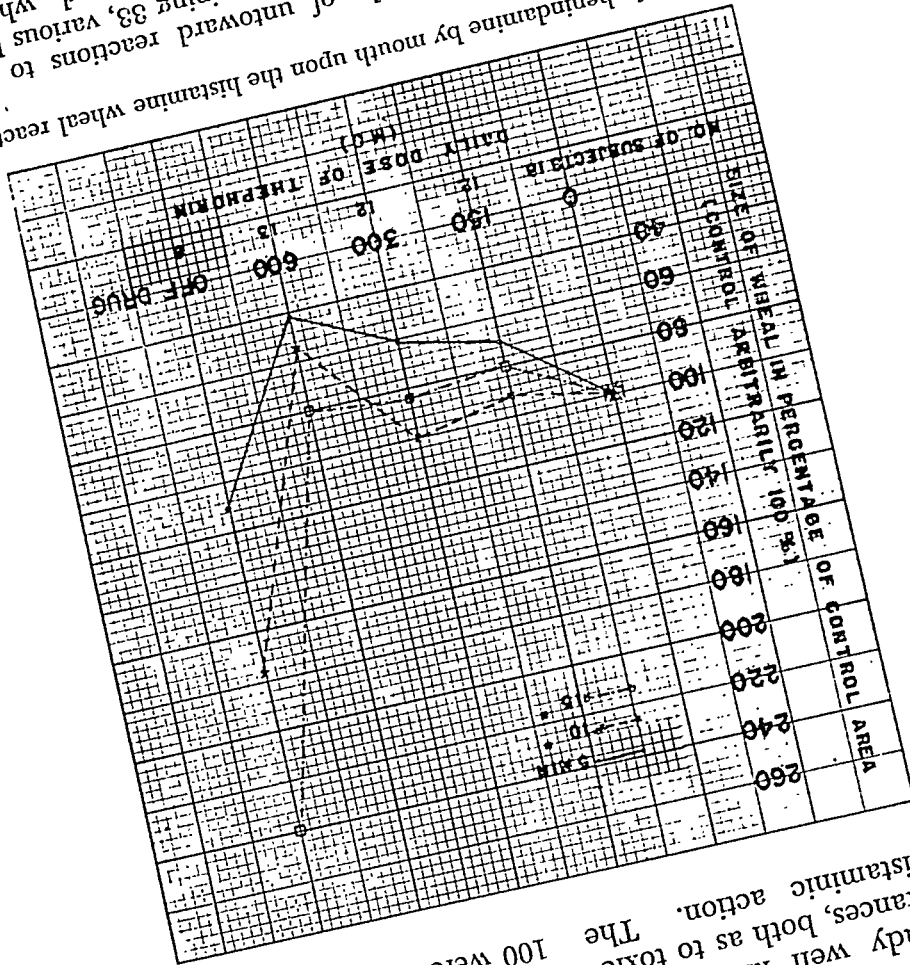
While a number of compounds of the types just mentioned have exhibited a high degree of histamine-blocking action, many unpleasant side-effects have occurred in their application at the bedside. This has resulted in a widespread effort to find other substances, which retain the antihistamine property, but lack in greater or lesser degree undesirable toxic side-effects.

Phenindamine represents a compound of strikingly different chemical structure (Fig. 1), which shows appreciable antihistaminic activity.<sup>2,3,7</sup> In protecting guinea pigs from death due to exposure caused by inhalation of histamine spray, this drug proved to be about eight times as potent as antistine, twice as effective as Benadryl and one-half as active as Pyribenzamine.<sup>7</sup> In acute poisonings of small

\*Generous supplies of Thephorin, the Hoffmann-La Roche brand of phenadamine, whose course was adapted to our own facility,\* was administered in the form of 25 mg. tablets in doses varying from 0.25 to 0.75 g.

\*Thephorin is here-with gratefully acknowledged.

**Fig. 1—The influence of phenidamine by mouth upon the histamine wheal reaction in the skin.**



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we have included not only people without recognizable disease, but also a limited number of subjects with chronic osteoarthritis, moderate arteriosclerosis, and those attending a general medical clinic for minor illnesses. In all instances, subjects with any allergic manifestation or probable involvement of the autonomic nervous system were excluded from the "normal" group. Of the normal subjects, 100 were used to ascertain the frequency of histamine and antihistaminic action. The

laboratory animals, it is one-third to one-half as toxic as Benadryl.<sup>2,3,7</sup> In other words, phenindamine represents an entirely new type of chemical compound which compares favorably in anti-histaminic substances, both as to toxicity and antihistaminic action.

from 75 to 600 mg. daily for periods varying from 1 to 20 weeks. For specific tests, such as glucose tolerance and electrocardiographic tracings unit doses of from 300 to 600 mg. were used.

**Results. I. THE ANTIHISTAMINE EFFECTS OF PHENINDAMINE.** Indices of the antihistamine action of phenindamine were its influence upon (1) the histamine wheal-and-flare reaction in the skin and (2) gastric acidity following a 7% alcohol meal.

tions of the wheal-and-flare reaction were made. Twelve of the subjects were successively given 150, 300 and 600 mg. daily for periods of two weeks at each dosage level, while the remainder of the subjects were utilized at one or more levels of administration for varying periods of time.

The method for performing these tests has been previously described.<sup>1</sup> Readings and measurements were made at the end of 5, 10 and 15 minutes. Each subject served as his own control.

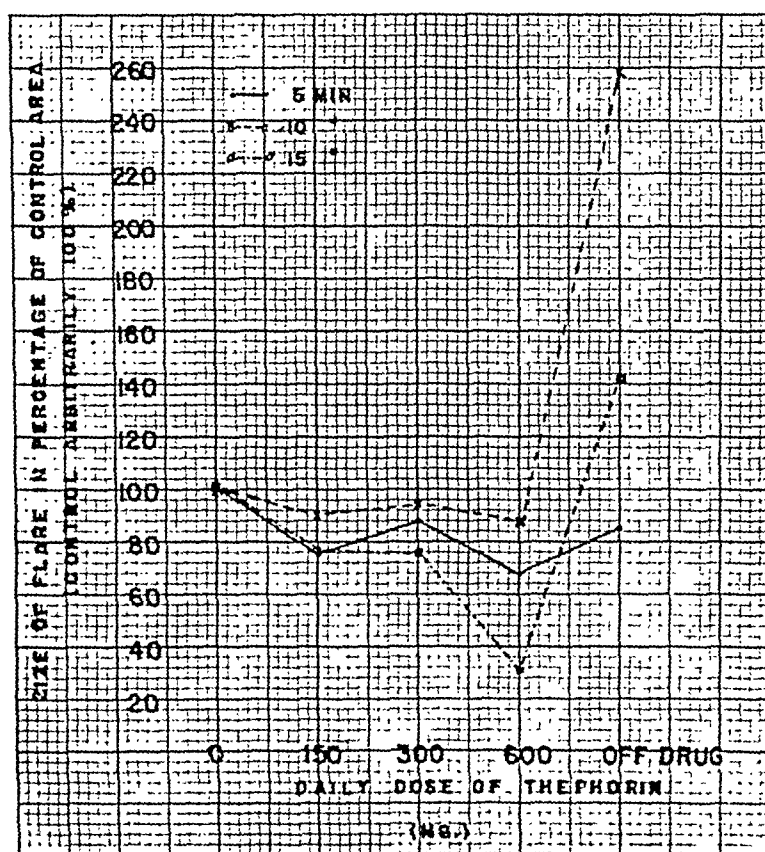


Fig. 2—The influence of phenindamine by mouth upon the histamine flare reaction in the skin.

1. *Changes in the response of the skin to histamine following the oral administration of phenindamine.* In 76 tests, the wheal-and-flare responses of 18 normal subjects were recorded following the oral administration of phenindamine in doses of 150 to 600 mg. daily for periods varying from one to eight weeks. In all, 76 determina-

Composite graphs of the areas of the wheals and flares thus obtained have been recorded in Figures 1 and 2 as percentages of the control values. Increasing doses of the drug influenced the size of the flare less than the size of the wheal, and at no dosage level was it possible to make these phenomena disappear routinely.

Several comments regarding individual responses may be apropos. In 15 subjects there was a steady decrease in the size of the wheal and flare as the dosage was increased, although the degree of change was always most marked with the initial dose of 150 mg. daily. In 2 subjects the dermic response to histamine was not appreciably altered by the oral use of phenindamine in the manner described, and in 1 the intensity of the reaction actually increased in spite of the drug. Of the 8 subjects studied in the "release" phase, *i.e.* one week after the drug was discontinued, 6 showed a dramatic increase in the size of the wheal and flare, while two developed responses similar to those seen in the control period. In two subjects there was complete suppression of the histamine flare while 600 mg. of phenindamine was being administered daily; in no instance was there a complete disappearance of the whealing phenomenon.

2. *Changes in gastric acidity following the oral administration of phenindamine.* 26 fractional gastric analyses following a 7% alcohol meal were performed on 6 subjects before and after the oral administration of phenindamine. In 4 subjects, the determinations were made before and after one week or more of treatment with each of the following daily doses of phenindamine: 75, 150 and 300 mg., respectively.

The values for gastric acid, both free and total, were lower in two subjects after two weeks each on 150 and 300 mg. daily of drug. In two more, the figures were at first lower, and in later tests higher than they were initially. In the remaining two subjects, there was no appreciable change in gastric acidity following the administration of phenindamine.

II. NON-SPECIFIC EFFECTS OF PHENINDAMINE. A total of 33 normal subjects were used in ascertaining the ability of phenindamine to influence various bodily functions. Unless otherwise specified the drug was given for prolonged periods of time at various levels of dosage, ranging from 75 to 600 mg. daily.

1. *The influence upon glucose tolerance.* Glucose tolerance tests were completed in relation to a single large dose of phenindamine in 9 instances, and after prolonged administration in 3 subjects. In 9 subjects, sugar tolerance was determined before and after the oral administration of a single dose of 300 mg. of phenindamine. The results have been described elsewhere in detail.<sup>6</sup> A similar study was attempted in 6 additional subjects following a single orally given dose of 600 mg. However, in each instance, the individual became nauseated and vomited before the test could be completed. Suffice it here to say that there were no appreciable changes in glucose tolerance as a result of such unit doses of phenindamine.

Three subjects were successively given daily doses of 75, 150, 300 and 600 mg. of phenindamine, respectively, for periods of not less than one week at each level of dosage. Before any drug was given and at the end of each period, an intravenous glucose tolerance test was performed. The results are graphically recorded in Fig. 3. It will be observed that no essential changes occurred in the glucose tolerance of these individuals as a result of the action of the antihistamine agent.

2. *Influence upon the basal metabolic rate and the cardiovascular system.* Serial determinations of the basal metabolic rate obtained in 33 subjects on a previously described regime of

living<sup>5</sup> were within normal limits following the use of phenindamine in widely varying doses (75 to 600 mg. daily) for periods of time ranging from 1 to 18 weeks.

The pulse rate, the blood pressure and the electrocardiograms of 30 normal subjects were not disturbed by large single or varying multiple doses of phenindamine.

3. *Alterations in the formed elements of the blood.* From Table 1 it is clear that the prolonged administration of phenindamine produces no significant changes in the blood count of normal subjects irrespective of levels of dosage between 75 and 600 mg. daily. The same statement may be made for all patients with allergic diseases in whom serial examinations of the blood were possible.

4. *Chemical determinations upon the blood serum.* As may be observed in Table 2, phenindamine employed over

a wide range of dosage and for varying periods of time failed to cause significant alterations in the following determinations on blood serum: icteric index, the thymol turbidity, the alkaline phosphatase, protein and protein partition, urea nitrogen, creatinine, glucose, cholesterol and cholesterol esters. Van den Bergh reactions, not recorded in this Table, were routinely negative.

III. EXPERIENCES WITH PHENINDAMINE IN THE TREATMENT OF ALLERGIC DISEASES. In all, 136 patients with some In all, 136 patients with some type of allergy have been treated with phenindamine. The results are summarized in Table 3.

1. *Hay Fever.* Of 66 patients treated, 13 (20%) were not helped, 41 (62%) were partially relieved, and 12 (18%) obtained complete relief. Inasmuch as the severity of hay fever varies directly with the pollen count

TABLE 1. BLOOD COUNTS IN HEALTHY SUBJECTS FOLLOWING ADMINISTRATION OF PHENINDAMINE IN VARYING DOSES FOR LONG PERIODS OF TIME\*

No. subj.	No. deter- mina- tions	Phenindamine dosage		Hgb. (gms./ 100 cc.)	Erythro- cytes (mill./ cu. mm.)	Leuco- cytes (thou./ cu. mm.)	Differential Count (%)				
		Daily (mg.)	No. days used (aver- age)				P	L	M	E	B
18	23	0	7 or more	13.8 (11-17)	4.32 (3.89- 5.30)	6.12 (4.55- 13.6)	57.8 (40-80)	36.7 (15-58)	4.0 (0-12)	1.45 (0-8)	0.05 (0-1)
1	1	75	7	13.0	4.50	7.50	60.0	35.0	3.0	2.0	0.0
1	1	100	5	15.0	4.37	5.40	70.0	28.8	1.0	0.0	0.2
12	28	150	31	13.6 (11-16)	4.19 (3.90- 5.00)	6.71 (5.10- 9.20)	54.6 (43-73)	42.7 (19-49)	2.2 (1-5)	1.2 (0-6)	0.5 (0-3)
1	2	200	14	13.5	4.15	7.53	67.3	30.0	2.0	0.7	0.0
13	26	300	21	13.6 (11-17)	4.20 (3.70- 6.20)	7.60 (5.50- 11.30)	63.8 (47-80)	32.2 (20-40)	2.7 (0-7)	2.3 (0-7)	0.1 (0-1)
6	8	600	7	13.3 (12-14)	4.40 (3.70- 4.50)	8.30 (6.30- 10.50)	56.0 (39-67)	40.5 (30-60)	2.4 (1-5)	1.0 (0-4)	0.1 (0-1)

\* Figures in parentheses represent the range of values.



TABLE 2. CHEMICAL ANALYSES OF BLOOD SERUM FOLLOWING THE ADMINISTRATION OF PHENINDAMINE TO NORMAL SUBJECTS

No. Subj.	No. deter- minations	Phenindamine Dosage		I.I. <sup>1</sup>	T.T. <sup>2</sup>	A.P. <sup>3</sup>	Protein <sup>4</sup>			Urea N <sup>5</sup>	Creat- inine <sup>5</sup>	Glu- cose <sup>6</sup>	Cholesterol <sup>5</sup>	
		Daily (mg.)	No. Days Used (Aver- age)				Total	Alb.	Glob.				Total	Esters
15	24	0	7 or more	5.4 (4.9- 8.3)	2.4 (0.4- 12.5)	3.1 (0.9- 12.0)	6.6 (5.0- 8.5)	4.3 (3.2- 5.4)	2.3 (1.3- 4.4)	12.9 (9.7- 22.5)	1.3 (0.8- 2.1)	105 (80- 120)	230 (160- 300)	145 (90- 200)
2	2	75	7	5.2	0.6	3.0	7.2	4.7	2.5	11.5	1.2	108	244	164
1	1	100	7	5.1	1.9	4.0	7.0	4.0	3.0					
10	21	150	35	5.4 (5.0- 6.0)	2.8 (0.3- 13.6)	4.6 (2.0- 6.0)	7.1 (5.6- 8.9)	4.5 (2.8- 6.0)	2.6 (1.6- 3.0)	12.7 (6.8- 23.5)	1.3 (0.8- 2.1)	103 (83- 127)	228 (185- 350)	149 (70- 220)
1	2	200	14	7.3	2.7	5.5	7.7	4.7	3.0	16.8	1.6	94	250	160
12	18	300	21	5.8 (5.0- 9.2)	1.7 (1.0- 3.4)	4.2 (1.0- 10.2)	7.1 (6.0- 9.0)	4.6 (3.5- 6.0)	2.5 (1.5- 4.4)	12.7 (7.0- 17.0)	1.3 (0.9- 2.3)	105 (83- 116)	224 (146- 340)	146 (100- 230)
10	17	600	7	5.3 (5.2- 5.7)	1.8 (0.9- 2.7)	4.4 (3.0- 7.0)	6.9 (5.2- 7.8)	4.5 (3.5- 5.6)	2.4 (1.5- 3.3)	12.8 (9.5- 15.9)	1.4 (1.1- 2.1)	100 (87- 109)	206 (164- 272)	142 (110- 182)

<sup>0</sup> Figures in parentheses represent the range of values.

<sup>1</sup> I.I.=Icteric index

<sup>2</sup> T.T.=Thymol turbidity

<sup>3</sup> A.P.=Alkaline phosphatase

<sup>4</sup> Expressed in per cent

<sup>5</sup> Expressed in mg. per 100 cc.

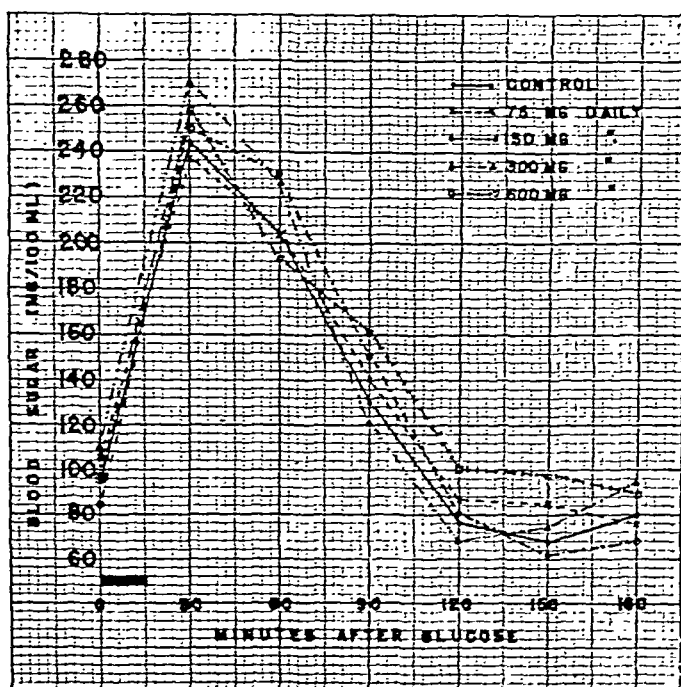


Fig. 3—Averaged glucose tolerance curves in 3 subjects before and after treatment successively with phenindamine in the daily dose noted. (Each dosage level was continued for at least 1 week in each subject).

in the air, we ran simultaneously a series of control observations in patients to whom a placebo was administered; 5% of these controls were symptom free, 30% improved while taking placebo and 61% remained in *statu quo*. In order to evaluate the results in terms of an antihistamine substance of known potency, a number of patients were given Benadryl and observed concurrently with those receiving phenindamine. Of these, 21% obtained complete relief, 59% partial relief and 20% no relief.

observed in each of 7 patients. These necessitated the discontinuance of the drug in two who received 75 and 250 mg. daily, respectively.

3. *Bronchial asthma*. Only 1 of 24 cases of bronchial asthma was relieved through the use of phenindamine (Table 3). However, in most instances, patients received the drug only at the time of their attacks. In 4 subjects, phenindamine was tried in a dose of 200 mg. daily as a prophylactic against attacks. In this connection it proved to be far inferior to Benadryl, the mild

TABLE 3. RESULTS OF TREATMENT WITH PHENINDAMINE IN 136 PATIENTS WITH ALLERGIC MANIFESTATIONS

Condition	Total	CR*		Result I*		NR*	
		No.	%	No.	%	No.	%
Hay fever	66	12	18.2	41	62.1	13	19.7
Allergic Rhinitis	25	5	20.0	9	36.0	11	44.0
Asthma	24	1	4.2	4	16.7	19	79.1
Urticaria—acute	16 3	6	37.5	8	50.0	2	12.5
Miscellaneous	5	1	20.0	2	40.0	2	40.0
Totals	136	25	18.4	64	47.1	47	34.5

\* C.R.=Complete relief,  
I.=Improvement and  
N.R.=No relief

Phenindamine was employed in the hay fever subjects for periods of from 15 to 120 days in daily doses of from 75 to 150 mg. Side effects were present in 22 of the 66 patients, but in 6 were so mild as to disappear while the same daily portion of drug was continued.

2. *"Vasomotor Rhinitis."* Of 25 subjects with this condition (Table 3), 5 (20%) were completely relieved, while 44% were unimproved. All patients were started with 75 mg. of the drug daily; if there was no appreciable effect, the dose was increased until improvement occurred or until 250 mg. were used daily without relief. The periods of observation varied from 7 to 120 days. Some side effects were

sedative and moderate antispasmodic action of which often protects the asthmatic completely for such time as it may be continued.

Seven of the 24 subjects showed some mild reaction to the drug, in no case sufficiently distressing, however, to prevent continuation of treatment.

4. *Urticaria*. Three of the 16 cases of urticaria were acute and 13, chronic (Table 3). It was difficult to tell with certainty whether or not the drug influenced the acute cases, although a clinical impression prevailed that the course of the condition was shortened. Of the chronic cases, complete or partial relief occurred in approximately 87.5% on daily doses ranging from 75

to 150 mg. Improvement occurred neither as rapidly nor as completely as with Benadryl to which the pruritus always yielded, probably in part due to its mild sedative action.

5. *Miscellaneous conditions.* Two cases of contact dermatitis were improved by phenindamine in daily doses of 75 and 100 mg., respectively, continued for 14 and 25 days, respectively. One patient with Fox-Fordyce's disease, in whom the itching was previously controlled by Benadryl, obtained no relief from phenindamine. One patient with a food allergy was not relieved following 14 days of treatment

ranging from 75 to 600 mg. for periods of from 1 to 6 weeks have been fully detailed elsewhere.<sup>9</sup> 42% of the group evidenced some untoward effect. The incidence varied directly as the dose of drug used. When 75 mg. were taken daily, approximately 15% showed some reaction. With the average therapeutic dose of 150 mg. daily, the incidence of side reactions was 25.0%. When used in similarly selected and treated subjects, the corresponding incidence of reactions to Benadryl and Pyribenzamine was 64% and 64%, respectively.

The incidence of symptoms due to phenindamine in the descending order

TABLE 4. SIDE EFFECTS IN 34 PATIENTS RECEIVING THERAPEUTIC DOSES OF PHENINDAMINE

<i>Symptom</i>	<i>No. times observed</i>	<i>Symptom</i>	<i>No. times observed</i>
Dizziness	11	Headache	2
Drowsiness	9	Cough (?)	2
Dryness	9	Palpitation	2
Insomnia	7	Abdominal cramps	1
Nausea and vomiting	5	Nervousness	2
Blurred Vision	4	Weakness	2
		Anorexia	1
		Total.....	55

with 75 mg. daily. One patient with migraine of undetermined etiology was improved by unit doses of 25 mg. given in the very beginning of the individual attack.

IV. TOXIC EFFECTS OF PHENDAMINE. The toxic reactions to phenindamine were recorded in a group of selected subjects and in all of the patients who received the drug therapeutically. One hundred subjects were included in the first study; they were chosen with a view to eliminating allergic conditions and any disturbance of the autonomic nervous system. The results with this group of subjects, who received daily doses of phenindamine

of their frequency was dryness of the mouth, insomnia, constipation, dizziness, jumpiness or jitteriness, burning of the conjunctivae, intestinal cramps, drowsiness, weakness, and palpitation. Five subjects refused to continue the drug because of the severity of the side effects, but in none of these was the dose less than 300 mg. at the time it was stopped. In the smaller doses, insomnia and gastrointestinal symptoms were in the foreground. Most of the sensorial and circulatory symptoms occurred only when the largest doses were used.

Of the 136 patients who received phenindamine in a therapeutic range of

dosage (75 to 250 mg. daily), 34 developed some unpleasant manifestation, and enumerated a total of 55 complaints attributable to these side reactions (Table 4). These are recorded in the descending order of their frequency in Table 4.

**Discussion.** Phenindamine differs in chemical structure and in pharmacological action from the majority of antihistamine substances previously used in clinical medicine. In the latter regard, quite in contrast, for instance, to Benadryl and Pyribenzamine, it antagonizes the pressor responses to epinephrine, an action completely independent of its antihistamine effects.

From our observations to date, several conclusions may be drawn regarding its clinical application in allergic states:

1. It is about one-half as toxic as Benadryl and Pyribenzamine.

2. For the most part it lacks the sedative action of Benadryl and does not share its weak atropine-like effect.

3. In the management of hay fever, it is approximately as effective as Benadryl.

4. In both vasomotor rhinitis and in asthma it is less useful than Benadryl, although in selected cases proves of value where the latter causes extreme drowsiness.

5. Satisfactory relief is obtained in a high percentage of the cases of chronic urticaria, although equal results have

been reported with Pyribenzamine and better results with Benadryl. However, both the latter drugs have a greater tendency to undesirable side effects which may make phenindamine the drug of choice in many patients.

**Summary.** 1. Phenindamine (2-methyl-9-phenyl-2, 3, 4, 9-tetrahydro-1-pyridindene) represents a new type of compound with an overall antihistaminic activity in the human being which is about one-half to two-thirds that of either Pyribenzamine or Benadryl.

2. The allergic diseases which have responded to its application include hay fever, acute and chronic urticaria, and vasomotor rhinitis, somewhat in the order named. In these regards, its action follows the general pattern already observed for such commonly recognized antihistaminic compounds as Benadryl and Pyribenzamine.

3. The overall incidence of reactions to the use of phenindamine lies between 25 and 40% or about two-thirds to one-half that observed for either Benadryl or Pyribenzamine.

4. It seems likely from present comparative observations that no one antihistaminic substance will be useful in *all* cases where such compounds are applicable, but that individual variations from patient to patient may justify a "trial and error" method of selecting the most suitable preparation for the case in question.

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## GLUCOSE TOLERANCE: II. EVALUATION OF GLUCOSE TOLERANCE IN LIVER DISEASE AND COMPARISON OF THE RELATIVE VALUE OF THREE TYPES OF TOLERANCE TESTS

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Since Hamman and Hirschman<sup>16</sup> first described the one-dose oral ("standard") glucose tolerance test and suggested its use as a diagnostic aid in diabetes mellitus, many disease processes other than insulin deficiency have been shown to exhibit disturbances in carbohydrate metabolism resulting in a decreased glucose tolerance. As our knowledge of carbohydrate metabolism develops, it becomes increasingly apparent that the liver is particularly important in its regulation. This fact is brought to the fore in hepatic diseases, especially in cirrhosis. It is with this phase that we are concerned in our present study of 19 cases of cirrhosis, 3 of which were associated with cardiac failure, and of 10 cases of infectious hepatitis in various stages of convalescence.

The diagnosis in all cases of cirrhosis was proven not only by the clinical and laboratory manifestations, but also by liver biopsy obtained with the Vim-Silverman needle. There were no complications with this latter procedure. It is not our purpose to consider the pathogenesis nor the clinical manifestations of liver disease, but rather to investigate the ability of patients with hepatic disease to handle glucose as demonstrated by the alteration of the 3 common types of glucose tolerance tests in present use, *i.e.*, the one-dose oral ("standard"), the one-hour, 2-dose oral (Exton-Rose) and the intravenous.

We have attempted to ascertain which of these tests is most significant as an index of liver function in so far as carbohydrate metabolism is concerned and how it correlates with the clinical picture and with other liver function tests as an index of liver disease.

**Observations.** An evaluation of the patients, at the time of the present study, revealed that the general condition and prognosis of the 19 cases of cirrhosis was good in 6, fair in 4, and poor in 9. The ages ranged between 32 and 68 with an average age of 49 years. Thirteen of the 19 patients had a history of chronic alcoholism. The duration of symptoms ranged between 3 months and 11 years (average 2 years and 3 months). The most frequent complaints were abdominal discomfort (13 cases), weight loss (9 cases), jaundice (8 cases), shortness of breath (8 cases), weakness (7 cases), nervousness (6 cases), loss of appetite (6 cases), vomiting (5 cases), swelling of ankles (4 cases), cough (2 cases), and vomiting of blood (2 cases).

Hepatomegaly of a considerable degree was a prominent feature in the cases with cirrhosis which included those with far advanced disease and a poor prognosis. This finding is in contrast to the small liver described in the literature as being typical of advanced cirrhosis. Hepatic enlargement was termed minimal when the liver edge was palpable 2 to 3 cm., moder-

ate when 3 to 8 cm. and marked when over 8 cm. below the costal margin. Thus, according to these criteria, the hepatomegaly was marked in 10 of the cases of cirrhosis, moderate in 7, and minimal in 2.

The remaining clinical manifestations show fairly good correlation with those found in a similar series.<sup>13</sup> Spider angiomas were noted in 10 cases, ascites was noted in 7 cases, peripheral edema in 7 cases, and splenomegaly in 4 cases.

The patients with hepatitis were in various stages of convalescence. The prognosis and general condition was good in all. The duration of symptoms ranged between 4 weeks and 2 years (average 5 months). The average age, being 30, was considerably lower than that of the patients with cirrhosis. The most frequent complaints were jaun-

dice (seen in all patients and recurrent in 5), nausea, anorexia, low grade fever, right upper quadrant tenderness, and neurasthenic symptoms following the acute illness. Hepatomegaly was seen in 7 of the 10 cases initially and was present in 3 at the time of this study.

The results of certain liver function tests, other than glucose tolerance, performed on the patients are summarized in Table 1.

Although jaundice usually has not been considered a manifestation of cirrhosis,<sup>30,41</sup> 8 of the 19 cases, or about one-half had a definite history of jaundice. Moreover, 8 cases, 4 of whom had a history of jaundice, showed an elevation of the icteric index, at the time of this study, from minimal to moderate in amount, (Table 1). Foley *et al.*<sup>9</sup> reported elevated icteric indices in 20 of 21 cases of cirrhosis.

TABLE 1. LIVER FUNCTION STUDIES

Case No.	*BSP Retent.	Icteric Index	Ceph.Floc.		Thymol. Turb.	Proth. Time Pats.	Control	A/G Ratio	RBC	Liver Biopsy
			2 1/2 hrs.	48 hrs.						
1	14%	16	—	—	—	—	—	3.5/3.0	3.3	Mil. Cirrhosis
2	5%	8	0	0	—	—	—	3.5/2.8	4.0	Mil. Cirrhosis
3	12%	24	0	1+	0	10	15	4.0/2.3	4.0	Mil. Cirrhosis
4	14%	12	0	1+	9.5	26	15	3.4/3.2	3.3	Mil. Cirrhosis
5	17%	8	0	0	2	14	16	5.1/3.1	3.9	Mil. Cirrhosis
6	18%	10	1+	2+	4	14	17	3.0/2.8	4.1	Mil. Cirrhosis
7	18%	27	1+	2+	9.5	27	15	3.8/4.0	3.8	Mil. Cirrhosis
8	26%	42	2+	3+	15	24	17	2.1/4.2	4.1	Mil. Cirrhosis
9	29%	2	0	0	3.5	9	15	5.5/1.9	4.5	Mil. Cirrhosis
10	35%	12	0	0	0	13	18	3.2/2.5	4.15	Mil. Cirrhosis
11	22%	10	0	1+	—	18	14	3.9/4.1	2.2	Mil. Cirrhosis
12	10%	6	0	0	1	15	17	4.6/2.5	4.6	Mil. Cirrhosis
13	3%	8	0	0	—	41	18	4.0/2.7	3.5	Mil. Cirrhosis
14	10%	6	0	0	—	15	19	3.1/2.8	3.0	Mil. Cirrhosis
15	14%	20	0	0	—	23	17	4.0/3.0	3.2	Mil. Cirrhosis
16	34%	29	0	1+	2.5	21	16	4.0/3.7	4.2	Mil. Cirrhosis
17	11%	8	0	1+	5	17	16	—	4.4	Mil. Cirrhosis
18	29%	4	Neg	3+	4	15	17	4.4/2.3	4.2	Mil. Cirrhosis
19	30%	5	0	0	3	—	—	4.1/1.2	3.8	Mil. Cirrhosis
20	14%	24	—	—	5	15	15	4.3/3.4	4.2	Mil. Hepatitis
21	7%	6	0	0	2	14	15	4.3/2.4	4.6	Mil. Hepatitis
22	9%	4	0	0	9	19	16	4.1/2.4	5.0	Mil. Hepatitis
23	1%	5	0	0	0	14	18	4.1/3.4	4.3	Mil. Hepatitis
24	2%	4	0	0	0	17	18	4.4/2.8	4.5	Mil. Hepatitis
25	3%	12	0	0	0	15	18	4.0/3.0	4.4	Mil. Hepatitis
26	10%	18	—	—	—	20	16	4.1/2.9	4.5	Mil. Hepatitis
27	20%	16	0	1+	3	16	18	5.9/3.2	4.1	Mil. Hepatitis
28	41%	24	0	1+	16	17	18	5.0/2.5	5.4	Mil. Hepatitis
29	1%	17	0	0	0	—	—	—	4.5	Mil. Hepatitis

\* Determinations done 45 minutes after 5 mg. of dye per kg. of body weight was injected. Over 5% retention was regarded as abnormal by this laboratory.

The normal cephalin flocculation studies in such a high percentage of the cases may be due to the laboratory technique of this hospital since the very small number of patients with liver disease showing disturbances of this test has been noted by us previously.

Low serum albumin and anemia of some degree were the rule rather than the exception. This has been noted by others.<sup>13</sup>

The results of the 3 glucose tolerance tests as well as the post prandial blood sugar level have been tabulated for each patient in Table 2. The post prandial blood sugar was ascertained 2½ hours after the patient had been given a standard meal of 100 grams of carbohydrate, 35 grams of fat, and 35 grams of protein. The blood sugar estimations were obtained from venous blood after the method of Folin and Wu.<sup>10</sup>

TABLE 2. TABULATION OF BLOOD SUGAR LEVELS DURING 3 TYPES OF GLUCOSE TOLERANCE TESTS

Case	Diagnosis	Standard Oral Test					Exton-Rose			Intravenous Test					P.P.
		F.	½Hr	1Hr	2Hr	3Hr	F.	½Hr	1Hr	F.	½Hr	1Hr	2Hr	3Hr	
1	Cirrhosis	123	215	260	180	85	129	245	273	145	396	252	200	115	200
2	Cirrhosis	93	200	249	176	100	114	176	188	115	299	230	110	68	100
3	Cirrhosis	95	171	188	171	91	113	168	256	105	281	195	133	91	123
4	Cirrhosis	108	195	256	219	105	98	170	209	108	286	267	162	105	—
5	Cirrhosis	109	170	209	127	81	80	109	144	102	256	122	87	87	112
6	Cirrhosis	112	130	192	157	68	94	143	208	87	238	174	152	70	108
7	Cirrhosis	118	195	240	181	90	110	267	162	111	217	132	93	137	100
8	Cirrhosis	186	200	286	290	200	157	195	229	109	276	238	138	110	205
9	Cirrhosis	84	150	141	142	77	92	150	170	100	291	191	119	91	81
10	Cirrhosis	96	180	167	130	122	82	105	113	90	250	135	95	95	105
11	Cirrhosis	146	342	420	512	510	155	250	340	128	460	359	273	181	—
12	Cirrhosis	147	226	300	217	203	159	256	264	143	300	224	176	132	—
13	Cirrhosis	93	158	129	120	79	102	172	167	99	238	121	83	83	—
14	Cirrhosis	110	186	240	77	70	91	127	156	120	360	215	109	81	114
15	Cirrhosis	98	135	139	95	58	111	178	206	90	245	130	78	75	123
16	Cirrhosis	102	160	128	102	90	98	132	160	100	200	196	105	100	99
17	Cirrhosis	57	158	117	60	57	68	196	191	76	214	146	84	76	109
18	Cirrhosis	118	190	182	162	162	98	170	209	79	288	158	137	129	123
19	Cirrhosis	100	132	139	120	74	87	119	135	78	169	113	78	82	104
20	Hepatitis	76	114	191	162	143	100	165	261	91	214	176	91	100	113
21	Hepatitis	76	114	133	114	76	66	96	150	68	204	141	91	87	96
22	Hepatitis	104	122	128	113	96	113	149	133	109	200	105	96	109	79
23	Hepatitis	81	162	100	81	81	79	152	157	93	338	129	81	92	157
24	Hepatitis	117	156	139	117	111	104	138	135	95	280	135	65	90	76
25	Hepatitis	88	136	105	92	81	78	120	135	92	254	97	94	88	—
26	Hepatitis	102	241	219	118	118	105	192	196	103	244	169	115	96	150
27	Hepatitis	81	132	123	113	109	110	140	130	102	353	211	116	106	100
28	Hepatitis	91	121	227	87	71	83	120	145	85	170	105	100	95	110
29	Hepatitis	88	122	117	62	70	100	127	122	104	205	104	100	86	81
MEAN		103	172	185	148	113	103	164	184	101	264	171	116	98	—
Standard Deviation		25	47	73	85	83	23	44	54	17	66	59	42	23	—
Mean of 103															
Normal Controls <sup>29</sup>		96	145	128	95	82	97	138	131	96	223	126	88	91	98
Standard Deviation for Controls		11	25	30	15	16	10	25	34	11	69	41	13	13	18

The standard deviation was calculated by use of the following formula:

$$\text{St.D.} = \sqrt{\frac{\sum x^2}{N} - M^2} \quad M = \text{means}$$

Calculations made by Department of Biometrics, Randolph Army Air Field, Texas.

Each patient was placed on a diet of 280 grams of carbohydrate, 100 grams of protein, and 100 grams of fat for at least 5 days before any glucose tolerance tests were done in order to eliminate discrepancies due to dietary influences. Two days or more were allowed between tests.

**Techniques:** The standard glucose tolerance test was made by obtaining the blood sugar level in the morning, after 12 hours fasting, and again  $\frac{1}{2}$  hour, 1 hour, 2 hours, and 3 hours following the ingestion of 100 gm. of glucose dissolved in 600 cc. of water flavored with lemon juice.

The one-hour, 2-dose Exton-Rose test was done, by dissolving 100 gm. of glucose in 600 cc. of water and flavoring with lemon juice. A fasting blood sugar was then taken, following which half of the glucose (50 gm.) was given by mouth. A second blood sugar was taken after 30 minutes following which the remaining 50 gm. of glucose was ingested. A third blood sugar was then taken  $\frac{1}{2}$  hour later.

The intravenous glucose tolerance test was done by administering 0.5 gm. of glucose per kg. of ideal weight, in 300 cc. of normal saline. The glucose was given by intravenous drip over a minimum of 20 and a maximum of 30 minutes. Blood specimens were obtained in the fasting state and  $\frac{1}{2}$  hour, 1 hour, 2 hours, and 3 hours after the intravenous drip was started.

Table 3 shows an analysis and comparison of the number of cases showing decreased glucose tolerance in one or more of the 3 tests according to the criteria of various authors for interpretation of normality versus abnormality. Referring to Table 2, we note that in Cases 7 and 16 the 1-hour blood sugar values in the Exton-Rose test are 162 and 160 mg. per 100 cc. respectively. These, because of the small deviation, will be regarded as within normal limits according to the criteria of Mathews *et al.* (below 158 mg. (item 3, Table 3)), since in the opinion of the authors

such a sharp line of distinction does not exist. Under the same token, in Case 27, the 2 hour blood sugar level of 116 mg. per 100 cc. for the intravenous test, (criterion 5, Table 3), will be considered within normal range.

In an evaluation of the standard glucose tolerance test in these patients the maximum blood sugar, or "rise," was not taken to be indicative of abnormality since this value is too dependent on extra-metabolic factors such as gastro-intestinal absorption, etc. Joslin<sup>19</sup> states that a rise above 170 mg. per 100 cc. is abnormal. However, in the authors' experience,<sup>20</sup> and that of others, the maximum blood sugar concentration may be considerably more than 170 mg. in normal individuals. For example, in a series of 103 normal young male controls, 16 (15%) were found to have maximum blood sugar levels during the first hour of the standard test well in excess of 170 mg.<sup>20</sup> When the mean value plus or minus twice the standard deviation was used for determining the range of blood sugar, it was found to be 95 to 195 mg. for the 30 minute sample, and 68 to 188 mg. for the one hour sample, as compared to 65 to 125 mg. by the second hour. Standard deviation values of 25 for the  $\frac{1}{2}$ -hour, 30 for the 1-hour, as compared to 15 at 2 hours, likewise attest to a wide range of normality during the first hour.

The criterion of Gould *et al.*,<sup>14</sup> for the standard test, *i.e.*, 3 hour blood sugar below the fasting level, is included in Table 3 for comparison. This criterion, also apparent in the small series of liver disease, is of value in estimating the severity of disturbance of carbohydrate metabolism as shown by the authors elsewhere<sup>20</sup>; but is too insensitive as an absolute criterion, and for that reason will not be included further in this discussion.



The criteria for a normal standard tolerance test, as outlined by the authors (item 7, Table 3), so nearly parallel those of others,<sup>8,11,12,15,16</sup> as outlined in item 1, Table 3, that the latter will be used in further discussion, *i.e.*, fasting and 2-hour blood sugar below 120 mg. per 100 cc.

In comparison of the 3 tests the criteria used for a normal intravenous test are those found by the authors on 103 controls<sup>29</sup> *i.e.*, normal fasting blood sugar and 2 hour value below 115 mg. (Table 3). However, these same values were arrived at by Lozner and associates<sup>23</sup> who found the normal range of the 2 hour blood sugar to be up to 90 mg. In their blood analysis, however, they used the Somogyi zinc precipitation method which determines fermentable "true sugar" levels. These average 10 to 30 mg. below the levels found by Folin-Wu tungstate precipitation<sup>19</sup> used by the authors. Using the latter analytic technique in their studies,

Lozner *et al.*<sup>23</sup> could expect the 2-hour blood sugar to range up to 115 mg. per 100 cc.

In evaluating the 1-hour, 2-dose test in this series of cases, the criteria of Matthews and coworkers (criterion 3, Table 3)<sup>26</sup> were used. According to these authors, they are more specific than the criteria of Exton and Rose (criterion 4, Table 3)<sup>8</sup> thus resulting in fewer false positives. Our viewpoint, developed as a result of comparative tests run on 103 normal subjects,<sup>29</sup> coincides. Duncan further states in his book *Metabolic Diseases* that the criteria of Matthews *et al.* are the most widely accepted today where the 1-hour, 2-dose test is used. This conclusion is supported by Table 3 in which 22 cases show abnormalities according to the criteria of Exton and Rose as compared to 15 cases by the criteria of Matthews and associates and 14 cases when the standard test is used for evaluation.

TABLE 3. COMPARISON OF ABNORMAL RESULTS ON THREE TYPES OF GLUCOSE TOLERANCE TESTS DEPENDING ON CRITERIA USED

CRITERIA	10 CASES CONV.		
	19 CASES CIRRHOSIS	HEPATITIS	TOTAL
**1. No. of cases with fasting or 2 hr. blood sugar above 120 mg. per 100 cc. on the standard oral test. <sup>8,11,12,15,16</sup>	13	1	14
2. No. of cases with 3 hr. blood sugar above the fasting level on the standard oral test. Gould <i>et al.</i> <sup>14</sup>	6	3	9
**3. No. of cases with abnormal fasting blood sugars or 1 hr. blood sugars above 158 mg. per 100 cc. on the Exton-Rose test. Matthews <i>et al.</i> <sup>26</sup>	13	2	15
4. No. of cases with abnormal Exton-Rose tests according to criteria of Exton and Rose. <sup>8*</sup>	17	5	22
**5. No. of cases with abnormal fasting or 2 hr. blood sugars above 115 mg. per cc. on the I.V. test. <sup>23,29</sup>	9	0	9
6. No. of cases with abnormal curves according to criteria of both #1 and #3.	10	1	11
7. No. of cases with abnormal standard curves according to authors' criteria of normal obtained on 103 controls <sup>29</sup> <i>i.e.</i> , fasting blood sugar below 120 mg. per cc. and 2 hr. blood sugar below 125 mg. per cc. <sup>***</sup>	13	1	14

\* Criteria of Exton and Rose for normal individuals are as follows:

1. Normal fasting blood sugar

2. Rise in blood sugar of not more than 75 mg. per 100 cc. at  $\frac{1}{2}$  hour.

3. 1 hour sample not to exceed the  $\frac{1}{2}$  hour specimen by more than 5 mg.

\*\* Criteria used for interpretation of each test and for comparison of the three types of glucose tolerance tests, referred to in the discussion.

\*\*\* Conclusion reached by using the mean value (95.0 mg. for the 2 hour value)  $\pm$  twice the standard deviation (15.0)

Therefore, in further discussion and comparison of the 3 types of glucose tolerance tests, the criterion of item 1, Table 3, will be used for the standard 1-dose test; the criteria of Matthews *et al.* (item 3, Table 3) for the one-hour, 2-dose test, and the criteria of item 5, Table 3, for the intravenous test. The cases showing discrepancies between the 3 types of tests according to these criteria are tabulated in Table 4 along with the critical discrepancy values.

as having a definitely abnormal standard tolerance test with a normal Exton-Rose test. On the other hand, 4 (Cases 13, 15, 17, and 26 (Table 4)) had abnormal Exton-Rose tests with normal standard tests.

The intravenous test was within normal limits in all (Cases 5, 7, 10, 13, 15, 17, and 26), showing discrepancies between the standard and the Exton-Rose tests, and therefore was of little aid in evaluation of these discrepancies.

TABLE 4. CASES SHOWING DISCREPANCIES BETWEEN THREE GLUCOSE TOLERANCE TESTS EMPLOYED

CASE NO.	2 hr. BLOOD SUGAR STAND. TEST	1 hr. BLOOD SUGAR EXTON-ROSE TEST	2 hr. BLOOD SUGAR I.V. TEST
* 5	127 (Borderline)	144	87
* 7	181	162 (Considered normal)	93
*10	130 (Borderline)	113	95
**13	120	167	83
**15	95	206	109
**17	60	191	84
**26	118	196	115
*** 2	176	188	110
***20	162	261	91

\* Abnormal standard test because of a 2-hour blood sugar above 120 mg. per 100 cc. (item 1, Table 3) with normal 1-hour, 2-dose tests according to criteria of Matthews *et al.* and normal intravenous tests.

\*\* Abnormal 1 hour, 2 dose test with normal standard test, and normal intravenous test.

\*\*\* Abnormal 1 hour, 2 dose and standard tests with normal intravenous tests.

In the entire series of 29 patients, 9 had abnormal intravenous, one-hour, 2-dose, and standard tests. These, all of whom had cirrhosis, were the only patients showing abnormalities of the intravenous test. In addition, 9 patients showed discrepancies (Table 4) between the 3 tests. Thus, 2 patients (cases 2 and 20) had both abnormal one-hour, 2-dose and standard tests with a normal intravenous test. Three cases had abnormal standard tests and normal Exton-Rose tests. Two of these (Cases 5 and 10, Table 4) had 2-hour blood sugars of 127 and 130 mg. respectively on the standard test. These would be classified as borderline or presumptively diabetic. Therefore, only one (Case 7) would be classed

Because of reports in the literature<sup>6</sup> of the marked hypoglycemia in liver disease, particularly in the fasting state, this problem was studied further since our results did not seem to bear out this observation. Three cases of cirrhosis not included in this series of 29 were selected for 12 hour glucose tolerance tests to evaluate the fluctuation of blood sugar over a more prolonged period of time. The standard test was chosen since, in our experience, it seemed to be the most valid. The results are tabulated in Table 5.

**Discussion.** In the glucose tolerance tests in this series, it is apparent that the ability of patients with liver disease to handle glucose is altered in a high percentage of the cases regardless

of the type of test or criteria for abnormality used.

What part does the liver play in the normal glucose tolerance test?

The importance of hepatic glycogen storage seems well substantiated. Pachman<sup>30</sup> has found experimentally a substantial increase of liver glycogen following the oral test, but feels that this is not the only factor operative since tissue storage and utilization are also important. Moreover, Ravdin *et al.*<sup>33</sup> report that if the diet is deficient in carbohydrate, the liver becomes depleted of glycogen.

Employing the intravenous infusion

merely to diffusion into the tissues. Urinary excretion is apparently not an important factor since Pachman<sup>30</sup> found not more than 2 gm. to be excreted during the intravenous test in normal adults. There also is no change in respiratory quotient nor in basal metabolic rate to indicate increased oxidation.<sup>6,36</sup>

If the exact fate of administered glucose in the body is controversial, the regulation of this fate is even more so, particularly the role of hepatic function. Sweeney<sup>35</sup> concluded that the configuration of the normal glucose tolerance curve is due to increased se-

TABLE 5. BLOOD SUGAR VALUES OVER A 12 HOUR PERIOD AFTER THE INGESTION OF 100 GRAMS OF GLUCOSE

Case	F.	½h.	1h.	2h.	3h.	4h.	6h.	8h.	10h.	12h.
30	123	180	200	175	140	120	61	111	90	115
31	90	190	148	130	100	90	100	110	75	84
32	64	164	130	100	65	70	75	70	74	60

of glucose, Sosken *et al.*<sup>36</sup> in determining the amount of glucose entering and leaving the liver, found that it was stored in significant amounts during the first 2 hours. However, they did not determine the form in which it was stored. Thirty minutes after the intravenous administration of glucose, Palmer<sup>31</sup> was unable to find an increase of glucose in the liver. Ravdin further found that liver glycogen could be increased 84% by the administration of intravenous glucose, or 236% when forced feeding plus intravenous glucose was employed. In drawing conclusions from these results, the presumptive evidence is that a large part of the glucose taken orally or intravenously is metabolized in the liver as a storage product, glycogen or a closely allied compound. In addition, the tissue metabolic factor may play a considerable role.<sup>6</sup> McKean<sup>25</sup> further points out that a large factor in the sudden drop in blood glucose after the intravenous administration is due

cretion of insulin as a result of pancreatic stimulation following the administration of glucose, resulting in the rapid storage of glucose and a drop in blood sugar ensuing. The hypoglycemic phase was thought to be due to the over secretion of insulin.

In contrast, Soskin, Allweiss, and Cohn<sup>36</sup> obtained normal dextrose tolerance curves with the usual hypoglycemic phases in depancreatized animals which, before and during the experiment, were given a constant infusion of insulin and glucose in amounts which would maintain normal blood sugar levels in the fasting state. They concluded that the liver and its homeostatic mechanism was the all important factor in the rise and fall pattern of the normal glucose tolerance curve and not the variation in insulin liberation by the pancreas. They further found that if enough liver was removed to cause hepatic insufficiency, any degree of diabetic glucose tolerance curve could be produced depend-

ing on the amount of insufficiency produced.

Further, emphasizing the importance of the liver factor in the regulation of blood sugar levels is the work of Mann and Bollman.<sup>25</sup> They found that a partially hepatectomized animal would not die from hypoglycemia, but that glucose tolerance was impaired, resulting in a diabetic type curve; whereas completely hepatectomized animals rapidly died of hypoglycemic shock even though the muscle glycogen content was normal. This latter finding, according to Peters and Van Slyke,<sup>32</sup> is due to inadequate phosphatase in the peripheral tissue to catalyze the phosphorylation and breakdown of the muscle glycogen into glucose for liberation into the blood stream.

Lewis and Izume<sup>21</sup> have shown experimentally that in animals with liver damage produced by hydrazine there is also a resultant failure of glycogen storage in the liver after a standard dose of glucose, resulting in a diabetic type of glucose tolerance curve. However, after a prolonged time these same animals developed a marked hypoglycemia. This observation was substantiated by McIntosh<sup>27</sup> in studies on animals with liver damage due to other hepatotoxic substances. Thus, there is failure on the part of the liver to remove dextrose from the blood when the sugar content is high and a failure to maintain normal levels when low; i.e., the homeostatic mechanism was severely disturbed. Lewis and Izume also found impaired conversion of amino acids into glucose. Conn *et al.*<sup>6</sup> minimized this factor in patients on an adequate diet. Other observers<sup>4,6,42</sup> have found glucose tolerance to be altered in infectious hepatitis as well as in liver damage secondary to burns.<sup>41</sup> Therefore, it seems well established that the presence of an ade-

quate amount of properly functioning liver tissue is necessary for the control of carbohydrate metabolism which depends on the balance between glycogenesis, glycogenolysis, and glyconeogenesis.

How may these findings be applied clinically to the understanding and evaluation of chronic liver disease?

Soskin<sup>35</sup> reported abnormal glucose tolerance in chronic liver diseases and suggested that glucose tolerance be used as a liver function test. Jacobi<sup>17</sup> has gone so far as to attempt to differentiate intrinsic liver disease from the extrinsic forms such as carcinoma and common duct obstruction. According to his observations, glucose tolerance is decreased in both types of disease; but in the intrinsic type of pathological changes, he found a continued rise in blood sugar after 3 to 4 hours when employing the oral standard one-dose test, while in the extrinsic liver disease, the curve is abnormally elevated, but tends to fall gradually. On the other hand, Wilson<sup>42</sup> has observed that extrinsic disease such as chronic, passive congestion and obstructive jaundice do not appear to alter glucose tolerance. Pachman<sup>30</sup> has further concluded that dextrose tolerance is not a satisfactory aid in the differential diagnosis of jaundice.

If one notes in Table 2 the marked variation of glucose tolerance in this series of patients with intrinsic liver disease, this latter conclusion of Pachman seems justified. The degree of impairment will depend on the amount of hepato-cellular damage and resultant functioning reserve, rather than the etiological background. Since in extrinsic liver disease the hepatocellular damage is at a minimum, in comparison to the damage present in intrinsic liver disease, less impairment of hepatic function would be expected in the former instance. However, the degree

of hepato-cellular damage in intrinsic liver disease is so variable, resulting in such notable variation of glucose tolerance as seen in Table 2, that it is understandable why this test would not aid in the differential diagnosis of jaundice. One might also note, as Pachman<sup>30</sup> has already done in his study, that there is apparently no correlation between the degree of icterus and the severity of glucose tolerance impairment in this series.

In addition Pachman<sup>30</sup> has concluded that dextrose tolerance is not a reliable procedure for indicating impaired hepatic function. This seems unjustified to us in view of our findings in this series, as well as the findings of others<sup>3,6,28,42</sup> who found the dextrose tolerance test to be a good index of hepatic function, although not a constant one, which compares quite well with other well known liver function tests.

It is granted, as noted by Mann<sup>24</sup> and Tunbridge and Allibone,<sup>40</sup> that glucose tolerance depends on many extra-hepatic factors; and that glucose tolerance alteration is not specific for any disease, since it has been noted to be abnormal in such varied pathological states as diabetes, hyperthyroidism, nephritis, rickets, obesity, arteriosclerosis, cancer, pituitary disorders, arthritis, etc.<sup>2,7,18,45</sup> However, if these facts are recognized and the patient is evaluated with this in mind, with proper dietary standardization before the test, it appears to us that glucose tolerance testing may afford considerable aid in evaluation of hepatic function. In Table 3, it is evident that in the 19 patients with cirrhosis, regardless of the criteria or type of test used, the incidence of impaired glucose tolerance compares quite favorably with the results of other liver function tests, (Table 1). This seems particularly pertinent to us, since glucose tolerance

testing involves the evaluation of a physiological process that normally takes place in the liver. Disturbance of glucose tolerance was not a notable finding in the patients convalescing from hepatitis.

Conn *et al.*,<sup>6</sup> attempting to evaluate glucose tolerance in chronic liver disease, have concluded that impaired carbohydrate utilization was one of rate rather than of total disability, since the blood sugar usually returns to normal in 4 to 5 hours. They found no explanation for the delay other than impaired glycogenesis since there was no change of basal metabolic rate or respiratory quotient to indicate change of metabolite or increase in the rate at which it was being utilized.

These workers have also noted in their studies that a fasting hypoglycemia was an outstanding and constant finding, apparently on the basis of decreased glycogenolysis, possibly a result of decreased glycogen storage. In referring to Table 2, one notes that this finding has not been duplicated in our series of patients. In an attempt to investigate further this factor, three 12-hour oral tolerance tests were done.

In Table 5 one notices the marked fluctuation of blood sugar over a 12 hour period after the ingestion of 100 gm. of glucose. This would seem to indicate instability of carbohydrate metabolic regulation or failure of the homeostatic mechanism of the liver. However, consistent hypoglycemia was not in evidence.

Jacobi<sup>17</sup> has noted other characteristics of the glucose tolerance curve in liver disease. In his study of 25 cases, the oral glucose tolerance test was flat, or had a high rise with a fall to normal within 2 hours. In contrast, Wilson<sup>42</sup> found that the curves of advanced cirrhosis were characterized by a low peak, a sudden initial drop, and a very delayed return to fasting level with

little if any change in cases of mild hepatic insufficiency.

However, when one critically examines Table 2, it becomes apparent that in this series there is no completely typical curve. Some curves are "diabetic," others are normal, while others are flat, and a few have a high peak with a sudden drop. The most common abnormality is the "diabetic type" curve which in some cases may continue to rise even after 3 hours. The curves in these cases apparently differ in no way from those found in mild to moderately severe "true pancreatic diabetes." One would ordinarily conclude from the fasting blood sugars and grossly abnormal curves that Cases 8, 11, and 12 had an absolute insulin deficiency as well as hepatic deficiency. In view of the complete evaluation of these patients as to age of onset, clinical picture and laboratory studies, it is the opinion of the authors that this was not so, but absolute proof to the contrary is lacking. None of the patients included in this series received insulin during their course of therapy despite the apparently severe disturbance of carbohydrate metabolic regulation. It should be kept in mind that the diagnosis in this series of cases was made not only on clinical grounds, but was confirmed by pathological examination of liver tissue.

What is the most practical and valuable type of glucose tolerance test to use as a liver function study?

By reference to Table 2 we see that post prandial blood sugars are only a crude method of evaluation of carbohydrate metabolism and a poor index of hepatic function.

Wilson,<sup>12</sup> using an intravenous test on a series of patients with chronic hepatoses, found a significant number of cases with decreased tolerance by comparison to a control series. However, Pachman<sup>50</sup> thinks that the oral

test is more significant and more physiological than the intravenous test. In his series, when the intravenous test was abnormal, the oral test was always abnormal, but frequently the oral test was abnormal and the intravenous test normal. This same fact is outstanding in the series being reviewed at present. In Table 3, it is evident that in 9 patients the intravenous test was abnormal according to the criteria used (item 5). The standard and the one-hour oral tests (using the criteria of Matthews *et al.*) were also abnormal in all these cases. In addition, 6 patients had abnormal standard tests (2 of which were borderline only (Table 4)), and 7 had abnormal one-hour, 2-dose tests. One should also note a tendency to blood sugar depression in the 3 hour specimen of the intravenous test as compared to the same time interval in the standard oral test, although the maximum blood sugar level was much greater in the former. It would appear that the intravenous test is less sensitive to minor alterations of glucose tolerance and should be reserved for occasions when the oral method is impractical or when evaluation of gastrointestinal absorption is a factor.

Evaluation of the standard test versus the one-hour, 2-dose test is more difficult. In reviewing Tables 2 and 3 one is immediately impressed by the number of cases showing decreased glucose tolerance when the oral test is used, regardless of which test is used and which criteria are employed for interpretation. Of the 19 cases of cirrhosis and 10 of convalescent hepatitis, 13 and 1 respectively showed abnormal standard curves. When the criteria of Matthews *et al.* are used for interpretation of the one-hour, 2-dose test, 13 patients with cirrhosis and 2 cases of convalescent hepatitis revealed decreased tolerance, 11 of which were also included in the above group with

abnormal standard tests. Of these 11 patients with both abnormal standard and one-hour, 2-dose tests, 9 also had abnormal intravenous tests as noted above, and 2 had normal intravenous tests. In addition to these 11 patients, if we refer to Table 4, we find 2 patients with borderline standard tests who had normal one-hour, 2-dose tests. Only one patient had a definitely abnormal standard test, with a normal one-hour, 2-dose test. On the other hand, 4 patients had abnormal one-hour oral tests with normal standard tests. Thus, although the series is definitely too small for significant statistical analysis, if we accept the standard test as a point of reference for comparison, these results would seem to indicate that the one-hour, 2-dose test is either too variable, or the existing criteria for interpretation are too rigid so that the accuracy of this test cannot be accepted as valid. Therefore, the standard oral test remains the most valid approach to the determination of glucose tolerance. This conclusion bears out a similar observation made by the authors on 103 control cases.<sup>29</sup>

**Conclusions.** 1. Carbohydrate metab-

olism is disturbed in chronic liver disease, resulting in decreased glucose tolerance.

2. The glucose tolerance test obtained following a standardized dietary preparation is a satisfactory method to aid in the evaluation of liver function and compares quite favorably with other methods in present use, having the advantage of being a physiological evaluation.

3. Although the standard, one-dose test and the one-hour, 2-dose test are somewhat comparable, the standard test is apparently the more valid in determining abnormalities of glucose tolerance. The intravenous test is inferior to the oral glucose tolerance test as an index of hepatic function and only under special circumstances is it of use as an adjunct to the oral test methods.

4. If a minimum of venipunctures is desired, the fasting and the 2-hour blood sugars, otherwise employing the technique of the standard test, would appear to be most valid.

5. The most efficacious procedure in drawing definite diagnostic conclusions of hepato-cellular pathology is the liver biopsy.

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# PROGRESS OF MEDICAL SCIENCE

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UNDER THE CHARGE OF

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## THE VISCERAL MANIFESTATIONS OF SCLERODERMA A REVIEW OF THE RECENT LITERATURE

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Visceral manifestations of scleroderma have been recognized for more than 50 years, but little attention has been paid to them in discussions of this disease either in dermatological or in general medical texts. Perhaps much of this relative inattention may be due to the infrequent occurrence of scleroderma but undoubtedly some of it is the result of general lack of appreciation of the multitudinous visceral manifestations such patients may present. Furthermore, it is assumed that the development of symptoms referable to one or another internal organ of a patient suffering from scleroderma does not necessarily imply that the lesion of the affected organ is sclerodermatous in nature, especially if there is little cutaneous involvement. Therefore, because detailing of the internal manifestations of generalized scleroderma may stimulate the internist to be on the lookout for cutaneous lesions of this process and alert the dermatologist

to the possibility of associated internal lesions, we propose to survey some of the recent literature dealing with these visceral complications of diffuse scleroderma.

The systemic character of scleroderma is suggested by the definition of this disorder given by Becker and Obermayer<sup>5</sup> which is a modification of that proposed by Ehrmann and Brünauer:<sup>16</sup> "Generalized scleroderma is not strictly a dermatosis, but rather a disease of the connective tissue of various organs and systems, the skin, subcutaneous tissues, the muscles, bones and joints, tendons and fascias, the serous surface, internal organs, endocrine glands and nervous system. The patient first notes the surface alterations, consequently the dermatologist is usually first consulted."

The variety and types of lesions found in scleroderma in the past are indicated by the findings in autopsies.<sup>16</sup>

The muscles show increased connec-

tive tissue, histologically (interstitial myositis). The muscle vessels show severe changes, even to localized arterial obliteration, proliferation of the media as well as thickening and round cell infiltration of the adventitia. The capillaries often appear like long solid cellular strands. The veins show only endothelial proliferation. The muscle bundles are secondarily altered and show vacuoles as well as signs of atrophy. Changes in the bones include fusions of the periosteum with the surrounding soft parts; the periosteum may be easily stripped or be bound down by young fibrous tissue. There are also changes in the bone cortex and marrow. The marrow may be aplastic so that hematopoietic tissue may regenerate in the spleen and enlarge it. The splenic blood vessels are also severely damaged. Similar changes occur in joints. All studies of the internal organs show the same features—edematous infiltration, cellular infiltration and proliferation of the connective tissue which is followed by atrophic changes in the parenchyma. Blood vessels of all types are badly damaged. In the older literature there are references to affection of the heart (endocardium, valves, pericardium and myocardium), lungs (increase in interalveolar connective tissue and severely damaged blood vessels); liver, kidneys and spleen, lymphatic vessel system (occlusion of ductus thoracicus as well as nodular formations in the lymphatics); thyroid gland (atrophy or gross changes, but microscopically demonstrable connective tissue increase, and blood vessel injury); nervous system, peripheral and central (neuritis and degenerative changes, increase in connective tissue and thickening of the nerve sheaths in peripheral nerves and various proliferative and degenerative changes in the central nervous system). Ears and eyes have also been

involved. The latter may show bilateral cataract as well as less serious involvement.

The recent excellent study of Goetz<sup>21</sup> shows the great variety of lesions a single patient may present. He found for example, that his patient had the following sclerodermatous changes: Raynaud's phenomenon and pin point ulcers in various digits; on the skin, scleroderma; telangiectasia and calcinosis; gastrointestinal complaints, dysphagia and symptoms referable to esophageal ulcer, with radiologic demonstration of dilatation of middle third and narrowing of lower third of the esophagus, esophageal ulceration, lack of peristalsis and stasis in the duodenum, small and large bowel, with dilatation of individual loops of small bowel and extreme narrowing of part of the large bowel (findings were confirmed at autopsy); atrophy and fibrosis of muscles, extensive myocardial fibrosis of unusual type which had given various clinical evidences of heart involvement; marked changes in the kidneys, liver, spleen and lungs; and constitutional and hormonal disturbances; that is, marked loss of weight, pigmentation, loss of axillary and pubic hair and amenorrhea.

In passing it may be noted that if the infectious cause of scleroderma as claimed by Wuerthele-Caspe, Brodtkin and Mermod<sup>22</sup> were established, the development of widespread lesions would be easy to understand. Furthermore, it may be stated that the diffuse involvement of the collagen system, such as is also seen in disseminated lupus erythematosus, dermatomyositis, periarteritis nodosa, need not imply a single cause for all these lesions though it strongly suggests a common pathogenetic denominator.<sup>1,2,3,4,5,6,60</sup>

Let us now consider what is regarded by dermatologists as diffuse or generalized scleroderma from the clinical

standpoint and also its relation to acrosclerosis.

In most cases of diffuse scleroderma the process starts on the hands and feet with a somewhat later and slower involvement of the face. Three stages can be distinguished clinically: the edematous, the indurative and the atrophic stage. The initial edema does not pit on pressure. The skin appears tense and cannot be folded. The face assumes a mask-like expression; the regular folds smooth out. In the second phase the skin hardens and stiffens. This is particularly pronounced on the fingers, on the dorsa of the hands and in the region of the ankles. Hyperpigmented and depigmented spots appear in this stage. In the third stage the tips of the fingers become smaller and pointed, and the fingers are immobilized in a flexed position. The face, the nose, the ears, and the lips become gradually smaller and thinner. Ectropion develops, due to atrophy of the lids. All mucous membranes of the mouth (tongue, hard and soft palate and gums) may be involved in the indurative and atrophic process. Ulcers, probably due to tension and deficient circulation, develop mainly on the finger-tips, the elbows and the ankles.

For the purpose of this review we have assumed that scleroderma and acrosclerosis are the same disease, though Sellei,<sup>65a,b,c,d</sup> O'Leary<sup>53</sup> and others maintain that they are different.

In addition to the specific sources of information to be mentioned, special note should be made here of 3 important contributors to our present knowledge. The chapter in Jadassohn's *Handbuch* by Ehrmann and Brünauer is the summary of the lifetime effort of Ehrmann in this disease. Paul A. O'Leary of the Mayo Clinic has with his collaborators devoted more than 20 years to the furtherance of our knowledge of scleroderma, and allied

diseases. Robert H. Goetz of the Department of Surgery, University of Cape Town and the Groote Schuur Hospital, Cape Town, has contributed a massive compilation of the knowledge of the visceral complications of this disease. Some of the views of these individuals are cited in extenso. No definite attempt is made to evaluate the various visceral manifestations from the standpoint of frequency of their occurrence or importance. Thus the extent of the discussion of a particular visceral manifestation in no way implies a special importance of that manifestation from the clinical or other aspect.

*Pulmonary Lesions of Scleroderma.* This subject has been reviewed recently by Dostrovsky<sup>12</sup> of Jerusalem, under the title of "Progressive Scleroderma of the Skin with Cystic Sclerodermal Changes of the Lungs." Previously pulmonary changes had been mentioned by Finlay,<sup>18</sup> von Notthafft,<sup>53</sup> Matsui,<sup>48</sup> Kraus<sup>39</sup> and Ehrmann and Brünauer<sup>16</sup> and Linenthal and Talkov.<sup>46</sup> More recently, references to pulmonary findings were made by Jackman,<sup>33</sup> Hale and Schatzki,<sup>27</sup> Weiss, Stead, Warren and Bailey,<sup>76</sup> Kanee,<sup>35</sup> Pugh, Kvale and Margulies<sup>61</sup> Goetz,<sup>21</sup> Getzowa,<sup>20</sup> Murphy Krainin and Gerson,<sup>50</sup> and Bevans.<sup>6</sup> Bevans points out that in one of her cases (Case 2) the anatomic lesions of the lungs were out of all proportion to the clinical and radiological findings. The vascular changes in the lungs were more extensive than those found elsewhere. In her other case (Case 1) the changes were slight and confined to the periphery of the lungs at the bases. She points out that although fibrosis of the lung is frequently described in general scleroderma, practically no mention is made of pulmonary insufficiency. Pugh and his associates believe that the pulmonary lesions of scleroderma have a

roentgenographic appearance which is distinctive though difficult to describe; their Figure 1 is labeled "Pulmonary fibrosis due to scleroderma."

In his detailed study, Dostrovsky<sup>12</sup> described peculiar pulmonary changes found in 3 cases of progressive scleroderma, reference to which had not been found in the literature. Because of pulmonary symptoms, 2 of the patients (Cases 1 and 3) were treated for tuberculosis. The roentgenograms showed peculiar changes of varying intensity, the correct interpretation of which was only made possible later by the autopsy findings. Getzowa<sup>20</sup> explained the formation of sclerotic cysts in the lungs as follows: "Disappearance of alveoli in the parenchyma and replacement by bronchiolar proliferation have taken place, the latter becoming

fibrous solidification, are not rarities. They probably represent the final stage of pulmonary sclerosis.

*Esophagus.* Esophageal complaints in patients with generalized scleroderma are relatively frequent and often an early sign of the disease. Olsen, O'Leary and Kirklin in 1945<sup>58</sup> summarized the data on cases reported in the literature to that time as follows:

Their own experience, based on 350 cases of scleroderma and acrosclerosis, added 36 cases (approximately 10%). Their differentiation of diffuse scleroderma from scleroderma with Raynaud's syndrome (acrosclerosis), was thought to be unnecessary by Lindsay, Templeton and Rothman,<sup>45</sup> since acrosclerosis is, according to them, identical with diffuse or generalized scleroderma with sclerodactylia. As Olsen, O'Leary

TABLE 1. SUMMARY OF DATA ON CASES REPORTED IN THE LITERATURE OF SCLERODERMA WITH ESOPHAGEAL LESIONS

Total cases reported .....	32
Sex: male 7, female 25.	
Dermatologic classification.....	27
Acrosclerosis .....	21
Scleroderma (generalized).....	4
Acute edematous scleroderma.....	1
Localized scleroderma.....	1
Roentgenologic features.....	24
Stenosis in lower part of esophagus.....	8
Retardation, lack of motility.....	11
Dilatation or cardiospasm.....	5
Esophagosopic features.....	8
Stenosis in lower part of esophagus.....	5
Changes restricted to esophageal walls.....	3
Cases with necropsy.....	8

progressively subject to cystic distention. The disappearance of alveoli is caused by a fibrous process of the alveolar walls, with subsequent dissolution."

Getzowa also described in addition to this "pulmosclerosis cystica," "pulmosclerosis compacta," consisting in disappearance of alveolar parenchyma as the result of progressive alveolar fibrosis without cyst formation. Dostrovsky believed that the pulmonary lesions were specific symptoms of the progressive scleroderma syndrome and that both types, cystic sclerosis and

and Kirklin did not separate the two in their analysis of the literature, the present discussion will perforce follow their line since careful dermatologic differentiation is not always possible from the data submitted. From their own material, they were convinced that esophageal disturbances occur almost exclusively in cases of acrosclerosis rather than in those of generalized or diffuse scleroderma.

The first reference to esophageal complaints (dysphagia) in acute scleroderma was made by Ehrmann<sup>55</sup>

whose monumental chapter with Brünauer in the Jadassohn Handbuch is a storehouse of information on this disease. He made an esophagoscopic study of the patient and observed changes in the esophageal wall. In 1916 Schmidt<sup>65</sup> reported the roentgenologic appearances in a patient suffering from scleroderma and dysphagia, and although he found no lesion, there was delay in passage of the barium into the stomach. In 1923 Schwarz<sup>66</sup> described esophagitis in scleroderma. In 1930 Nomland<sup>52</sup> observed dilatation of the esophagus by means of roentgen study. Rake<sup>63</sup> in 1931 described gross and microscopic post-mortem findings in a case of scleroderma in which there had been contraction in the lower end of the esophagus roentgenologically; 6 years earlier the organ showed dilatation, with no muscular hypertrophy. In its upper third erosions were present in an intact mucosa, but in the middle and lower thirds the mucosa was lacking (post-mortem digestion?). The submucosa was thickened and infiltrated with cells, chiefly mononuclear and polymorphonuclear in type. In 1932 Fessler and Pohl<sup>17</sup> reported regional stenosis in the lower end of the esophagus. They had also reviewed the literature to that time and found that the esophageal lesions had been called cardiospasm (Nomland), esophagitis (Schwarz), diverticulum (Ehrmann) and atony (Schmidt).

Other reports of from 1 to 36 cases (Olsen *et al.*) have appeared: Tsukada;<sup>73</sup> Kuré; Yamagata; Tsukada and Hiyoshi;<sup>40</sup> Hiyoshi;<sup>30</sup> Weissenbach *et al.*;<sup>78</sup> Hoelsli<sup>21</sup> (a thesis on functional disturbances and lesions of the esophagus in scleroderma); Weissenbach, Martineau, Bouwens, Pizon and Matteo;<sup>79</sup> Barasciutti;<sup>3</sup> Ochsner and DeBailey;<sup>54</sup> Dowling;<sup>13</sup> Goetz and Cole Rous;<sup>22</sup> Thomas;<sup>72</sup> Jackman;<sup>33</sup> Lindsay, Templeton and Rothman<sup>45</sup> (5 cases of lesions of the esophagus

in generalized progressive scleroderma with detailed literature); Weiss, Stead, Warren and Bailey;<sup>76</sup> Hale and Schatzki;<sup>27</sup> Kanee;<sup>35</sup> Pugh, Kvale and Margulies;<sup>61</sup> Bevans;<sup>6</sup> Olsen, O'Leary and Kirklin;<sup>58</sup> Goetz;<sup>21</sup> Rafsky and Herzig;<sup>62</sup> Schatzki;<sup>61</sup> and Dostrovsky.<sup>12</sup> The papers of Lindsay, Templeton and Rothman, Olsen, O'Leary and Kirklin, and of Goetz deserve full study by the reader.

There is general agreement in the literature that the esophageal processes associated with scleroderma are the result of the presence of sclerodermatous changes in the walls of the esophagus. While there may be differences resulting from individual variation in the patients studied, there is on the whole agreement upon the findings. Most of the patients suffering from scleroderma or acrosclerosis with esophageal disturbances are women. This may be merely a reflection of the greater incidence of scleroderma in women. Weissenbach *et al.*,<sup>77,80</sup> 16 of 18 cases were women; Hale and Schatzki, 15 of 22 patients were women; Olsen, O'Leary and Kirklin (literature) 25 female and 7 male; (personal cases) 36 cases—24 female, 12 male). The patients complain of progressive dysphagia in some cases early in the disease. Weissenbach *et al.*, however, believe that the dysphagia is an early symptom only if the face and oral cavity are involved early. Hale and Schatzki found that 15 of 22 patients had no definite swallowing symptoms, while dysphagia was present in 7. Lindsay, Templeton and Rothman noted considerable variation in the severity and the time of onset of esophageal symptoms and considered this as characteristic. Only one of their 5 patients volunteered any complaints referable to swallowing. In the remaining 4 cases the symptoms were brought out on questioning but

the pain and discomfort from the cutaneous lesions caused the difficulty in swallowing to be overlooked. These authors worked out changes in muscular movements observed by fluoroscope and their findings will be discussed later. Olsen, O'Leary and Kirklin found the esophageal disturbance responsible for the symptoms of which the patient complained primarily. Actually they believed the esophageal disturbance was most often a delayed manifestation of the disease (Cf. Hoesli). Goetz showed the range of symptoms referable to involvement of the esophagus as exemplified by the findings in one of his patients. "The esophageal disturbances in our patient consisted in difficulty in swallowing, the sensation of blockage behind the sternum associated with cramp-like burning pain; nausea and regurgitation followed by relief on vomiting."

The radiologic findings in the esophagus have long been reported on. Among those who have paid special attention to this aspect of the problem are Schmidt, Kuré *et al.*, Weissenbach *et al.*, Weiss *et al.*, Ochsner and DeBakey, Jackman, Goetz (Goetz and Cole Rous<sup>22</sup>), Lindsay, Templeton and Rothman; Olsen, O'Leary and Kirklin; Hale and Schatzki; and Schatzki.

In 1916 Schmidt<sup>65</sup> studied a patient suffering from scleroderma and dysphagia and noted delay in the passage of barium sulfate (15 minutes was required for passage of the barium into the stomach). Kuré and his associates<sup>10</sup> made roentgen-ray studies in 5 patients with scleroderma. Only 2 of them complained of dysphagia but in all there was great retardation in the passage of a test meal especially when the patient was in the dorsal decubitus position. The greatest delay was in the cardia. Weissenbach and his associates, using Kuré's technic, found in addition to the retardation of the bolus,

that the normal peristaltic movements were absent and that there were a gaping of the esophagus and a tendency for the barium meal to adhere to the walls of the esophagus. Weissenbach, Stewart and Hoesli<sup>80</sup> summarized the roentgenographic findings in their cases as follows: 1) normal morphologic appearance of the esophagus; 2) retarded and complete descent of the opaque bolus with partial adherence to the esophageal wall; 3) accentuation of findings in the recumbent position and 4) evidence of esophageal blockage in some cases without clinical and subjective symptoms. Lindsay, Templeton and Rothman on the basis of their 5 cases stated that the esophageal disturbances are characterized by "loss of peristalsis in the lower two thirds, with relaxation and mild dilatation of the lower two thirds down to the phrenic ampulla, and probably some atony of the cardiac sphincter. This occurs as a direct result of the sclerodermatic process. Difficulty in swallowing solids or liquids especially when in the lying position, due to delayed emptying of the esophagus, burning pain behind the sternum about an hour after meals, worse on lying down and particularly on lying on the left side, due probably to regurgitation of gastric contents into the esophagus, and resulting chronic esophagitis, chronic ulceration of the lower third of the esophagus, localized chiefly to the region just above the phrenic ampulla. This is probably a direct result of the esophagitis with sclerodermatic changes as a predisposing factor. Stricture formation in the later changes is limited to the region immediately above the phrenic ampulla of the esophagus."

Dilatation of the esophagus with retardation of barium at the cardia was noted by Rake,<sup>62</sup> by Nomland<sup>63</sup> and by Jackman,<sup>64</sup> as well as by Rafsky and Herzig<sup>62</sup> who spoke of cardiospasm.

Stenosis of the cardiac end of the esophagus has been noted fairly often (Dowling; Fessler and Pohl; Lindsay, Templeton and Rothman; Olsen, O'Leary and Kirklin; Weiss *et al.*). Goetz noted dilatation of the middle third of the esophagus, narrowing of the lower third; delay in emptying and residual food and mucus as well as ulceration.

The roentgenologic appearance of the esophagus in scleroderma has been the interest of Hale and Schatzki. These radiologists, during the 5 years

an abnormal esophagus. Eight patients who were without symptoms showed abnormalities. There was no correlation of the extent of the cutaneous and esophageal changes. While the roentgenologic appearances of the abnormal cases were not uniform, they showed a distinct pattern consisting mainly in delayed emptying, combined with a decrease in the peristalsis of the esophagus (Cf. Lindsay *et al.*). Olsen, O'Leary and Kirklin noted conclusive roentgenographic features in 15 cases.

TABLE 2. DATA CONCERNING THIRTY-SIX CASES OF ACROSCLEROSIS OR SCLERODERMA IN WHICH THERE WERE ESOPHAGEAL SIGNS OR SYMPTOMS

- I. 18 cases with positive roentgenographic or endoscopic observations
  - A. Age distribution: 34 to 61 years
  - B. Sex: female 13, male 5
  - C. Dermatologic diagnosis: acrosclerosis, 18
  - D. Roentgenologic diagnosis, 18 cases
    1. Esophageal dilatation or cardiospasm, 6
    2. Hiatal hernia, 9
    3. Negative results of examination, 3
  - E. Esophagoscopy diagnosis, 8 cases
    1. Hiatal hernia (corroborated roentgen diagnosis), 5
    2. Sclerodermic involvement in patient with esophageal dilatation (by roentgen study), 1
    3. Sclerodermic involvement of esophageal wall not shown by roentgenologic examination, 2
  - F. Passage of sounds, 7 cases
    1. Diagnosis and treatment of cardiospasm, 3
    2. Dilatation of stricture associated with hiatal hernia, 4
- II. 6 cases with negative roentgenographic findings and no endoscopic studies
  - A. Age distribution: 23 to 60 years (average 44)
  - B. Sex: female 2, male 4
  - C. Dermatologic diagnosis: acrosclerosis 4, scleroderma 2
- III. 12 cases with neither roentgenographic nor endoscopic studies
  - A. Age distribution: 17 to 66 years (average 35)
  - B. Sex: female 9, male 3
  - C. Dermatologic diagnosis: acrosclerosis 11, scleroderma (acute), 1

\* In 2 of these cases esophagoscopy examination demonstrated changes in the esophageal wall. In the remaining case a diagnosis of cardiospasm was made by passage of sounds.

prior to publication, studied the upper gastrointestinal tract of 22 patients with scleroderma of variable duration. As noted above, only 7 of the patients had definite dysphagia although in 6 of the asymptomatic group careful questioning disclosed that a sensation of material remaining in the mid chest and occasionally localized burning or pain following the hurried ingestion of food, or after eating a large meal had been noticed. Five of 7 with dysphagia had

Their findings are summarized in the table.

*Esophagoscopy* is rarely practiced on patients with scleroderma, according to Weissenbach, Stewart and Hoesli,<sup>50</sup> because of narrowing of the oral orifice and atrophy of the buccal mucosa. Nonetheless there are observations on a few patients obtained by this means. Ehrmann<sup>15</sup> noted thickening of the esophageal wall; Schwarz described esophagitis; Lindsay, Templeton and

Rothman in repeated study of 4 of their 5 patients found inflammatory changes in the lower two thirds of the esophagus, with a diffuse white membrane in the lower part of the esophagus, about 4 or 5 cm. above the diaphragmatic level. Goetz recorded spasm on withdrawal of a dilator which passed easily into the stomach. Olsen, O'Leary and Kirklin performed esophagoscopic examination in 8 cases, and passed esophageal sounds in 7 of the 18 cases in which roentgenographic or endoscopic evidence was conclusive, over previously swallowed threads.

Histologically the changes in the esophagus have been studied, by Rake; Weissenbach *et al.*; Kuré *et al.*; Freudenthal;<sup>19</sup> Lindsay, Templeton and Rothman; Goetz, and by Bevans, and Ochsner and DeBakey. All found erosion of the mucosa, thickening of the submucosa, hypertrophy of the muscularis mucosae and atrophy of the muscular coats. Thomas reported an acute ulcer in his case. Goetz was the first to describe leukoplakia and calcification. Other findings in Goetz's case were marked hypertrophy of the muscularis mucosae, the presence of lymphorrhages, the marked disintegrative changes in the muscular layers (myositis), the extensive involvement of the myenteric plexus. Freudenthal had described lymphorrhages as a feature common to the muscular lesions of both scleroderma and dermatomyositis. Clinically, 8 of Goetz's 13 cases were affected with similar changes. All 3 cases coming to autopsy showed chronic ulcers.

Bevans<sup>6</sup> found replacement of the mucosa of the esophagus by fibrinoid material, the submucosa sclerotic, muscle layers atrophic and extremely fibrosed (Cf. Rake).

Differentiation of the esophageal complaints must be made from cardio-spasm, hiatal hernia, shortening of the

esophagus as it occurs in persons who are obviously normal. Complete discussion of the differential considerations of these processes from the organic changes in the esophagus in scleroderma is contained in the study of Olsen, O'Leary and Kirklin.

*Lower Gastrointestinal Tract.* Relatively little mention has been made in the literature about involvement of the gastrointestinal tract in scleroderma. Goetz stated that when he and Cole Rous in 1942 reported their case of scleroderma with duodenal stasis, the first in which the features of small bowel lesions were demonstrated radiologically, they could find only 2 similar lesions in the literature (Kraus,<sup>39</sup> Rake<sup>63</sup>). Since then other reports have appeared. Hale and Schatzki and later Schatzki described the roentgenological appearance of the gastrointestinal tract in scleroderma. A summary of their findings follows:

*The Stomach.* The stomach was examined in 22 patients. In some cases there was considerable delay in emptying; in some there was spasm of the antrum. The authors thought the significance of these changes, however, is doubtful.

*The Small Intestine.* Four of the 18 patients in whom the small intestine was studied showed remarkable changes roentgenologically. In 1 of the 4 cases the intestinal symptoms and the appearance of the intestine stood in the foreground, and the presence of scleroderma was discovered later more or less accidentally, whereas in the 3 other cases scleroderma had been present for many years. The small intestine showed significant changes in 4 patients. There was localized widening, usually of the proximal loops, together with marked delay in the passage of barium through these dilated loops. Recognition of these changes



in the small intestine appears to be of particular clinical importance.

*The Large Intestine.* Two of the patients with scleroderma showed an unusual appearance in the large intestine which is difficult to explain on the basis of any other pathology, and the authors therefore assume that it is related to their scleroderma.

Pugh and his co-workers in 1945<sup>61</sup> also reported on a patient with gastrointestinal involvement. They found that peristalsis in the small intestine was definitely sluggish and segments were seen to remain without normal contractibility for a considerable period before ineffective peristalsis would begin again. The relative lack of contractibility was seen especially in the terminal portion of the ileum.

Bevans<sup>6</sup> has made a study of the pathology of scleroderma with special reference to the changes in the gastrointestinal tract. In both of her cases, the remainder of the gastrointestinal tract showed extensive, although patchy, changes. There was but little thickening of the submucosa in either case. There was diffuse dilatation of the colon demonstrated by barium enema in her Case 1 because of muscle atrophy. (Matsui mentioned hypertrophy of the muscularis mucosae but atrophy of the muscularis propria.) In Bevans' cases either no change in the muscularis mucosae or atrophy was observed. Edema was present in the muscularis adjacent to areas of muscle atrophy. This latter change is in accord with the general pattern of the disease as it is seen in the skin in the form of edema, indurations and atrophy. There were outstanding vascular alterations in the gastrointestinal tract. Bevans cites a third patient with diffuse scleroderma, under observation for 3 years in the Goldwater Memorial Hospital, who developed signs of intestinal obstruction. Adhesions be-

tween intestinal loops were found at operation. No point of obstruction was determined but the small intestine was diffusely dilated. Death followed 12 hours later but no autopsy was performed.

Goetz believes that the gastrointestinal lesions in cases of scleroderma are not as rare as the literature would make us believe and it appears from his cases that duodenal stasis is, like esophageal spasm, one of the earlier visceral manifestations of diffuse scleroderma. Five of his cases had identical pronounced changes in the intestinal tract. The most prominent radiological appearances were paralysis and lack of peristalsis particularly affecting the duodenum and the jejunum with localized widening of individual loops and breaking up of the barium. In one case this was so marked that there was a duodenal residue after 24 hours and in another case the dilatation involved the whole small bowel so that the diagnosis of paralytic ileus was made at the time and laparotomy contemplated.

In the large bowel the most characteristic lesion on radiological examination according to Goetz, was narrowing and rigidity and the appearance of sacculation. However, this narrowing may not be confined only to the large bowel and in one case Goetz saw it in the terminal ileum, simulating regional ileitis. When first observed, these features were very puzzling and disputable, but when at autopsy narrowing and dilatation could be confirmed in all cases it became evident that these changes had to be regarded as integral and important clinical features of scleroderma.

In one patient studied in detail there were the following pathologic changes: 1, marked atrophy of the bowel wall; 2, fibrous replacement of muscle fibres with occasional lymphocytic and plas-

ma cell infiltration; 3, prominence of the neuromuscular apparatus.

The prominence of the neuromuscular apparatus was accompanied by a conspicuous absence of ganglion cells and fibrosis in some cases. This suggested to Goetz that the motor activity of the bowel was interfered with by some intrinsic nervous disorder brought about by the affection of the intramural neuromuscular apparatus, similar to what he had seen to be the case in the esophagus. In this connection Goetz calls attention to the investigations of Rake (1926, 1927) and Etzel (1942) in cases of achalasia of the esophagus. These authors regularly found fibrosis of the myenteric plexus with poverty of ganglion cells. Etzel (1942) suggested vitamin B deficiency as the responsible etiological agent. However, none of Goetz's patients showed signs of any of the known vitamin deficiencies. Indeed, if any signs of avitaminosis had developed one would not have been surprised in a case which suffered from difficulty in swallowing for 14 years. However, the radiological appearances of the bowel are very similar to those of a vitamin deficiency. For this reason all of Goetz's patients were treated intensively with all known vitamins with no effect except in one case in which duodenal stasis was present before, but absent after treatment. In this patient leukoplakia of the esophagus was found, present ever since the time she first complained of dysphagia, achlorhydria was present. However, the blood was always normal.

In passing, it is worthy of note that little has appeared in the literature recently on hepatic involvement by scleroderma. For example, Harvier and Bonduelle<sup>28</sup> observed a case of progressive scleroderma with hepatelienal calcification and in 1934 Milbradt<sup>40</sup> presented a patient with atypi-

cal diffuse scleroderma with Osler's syndrome (telangiectasia) and hepatic disturbance.

*Cardiovascular Involvement.* A variety of circulatory lesions have been observed in generalized scleroderma, (Hektoen;<sup>29</sup> Masugi and Yä-Shu<sup>41</sup>). An outstanding feature of this disease is vasoconstriction. Specific, that is sclerotic, changes in the heart muscle due to proliferation of connective tissue between the muscle fibers, myocarditis, dilatation of the aorta, and pericarditis, are among the changes which have been reported in the older literature. Newer studies have re-emphasized the circulatory features of this disease and have lent additional support to the idea that scleroderma is more than a cutaneous process. However, the mere presence of a cardiac or vascular lesion in a patient with scleroderma does not of necessity establish the sclerodermatous nature of the circulatory system disease. On the other hand, Johnson<sup>34</sup> has added somewhat to the complexity of this relationship by emphasizing the disabling changes in the hands resembling scleroderma following myocardial infarction.

In contrast to disturbances of the gastrointestinal tract, clinical evidence of cardiac involvement may occur late in the course of the disease, but Weiss and co-workers<sup>76</sup> in their careful study of sclerodermal heart disease, noted that in 3 cases the appearance of cardiac symptoms preceded changes in the skin by as much as 2 years.

They conclude that the evidence from 9 patients points toward the interpretation that the myocardial lesions are an integral part of scleroderma. "The sequence involved in the development of the myocardial lesions were those of overgrowth of connective tissue, as in the skin, but the character of the connective tissue in the skin and myocardium in scleroderma was dif-

ferent. However, the changes in the 2 patients with scleroderma studied at post mortem examination were similar and differed in several significant respects from other varieties of myocardial scars. The pathologic observations together with the clinical data in the cases of the series indicated that scleroderma heart disease is a clinical and pathologic entity."

All of Goetz's patients suffered from dyspnea, orthopnea and cyanosis and one of them presented the picture of a black cardiac. The heart in most of his cases was small, the blood pressure and the cardiac silhouette normal. However, the diagnosis of scleroderma heart was made from the kymogram which showed marked blunting of the cardiac excursions.

Goetz noted that the histology of the heart in patients coming to autopsy at first sight appeared very heterogeneous, revealing 3 different types of lesions: 1, scattered foci of fibrosis in apparently normal muscle fibres; 2, frank fibrosis of the entire thickness of the myocardium extending from the pericardium to the endocardium; 3, a diffuse lesion showing marked disintegration of the muscle fibres which were interlaced with coarse bundles of connective tissue which was highly vascular.

This third lesion is obviously the forerunner of the second type. All intermediate stages were observed. From these observations it became evident that myocardial fibrosis was not the result of vascular interference. This was supported by the lack of sufficient pathological changes in the coronary arteries, the pattern of the fibrosis and the absence of hemosiderin pigment in the connective tissue. The earlier lesions of this fibrous replacement were observed in another case. They reminded Goetz of what has been described in early cases of dermato-

myositis as "angiomyositis." Detailed findings indicate that the heart lesion is an integral part of scleroderma.

Despite the marked fibrosis the electrocardiogram did not show great change in one of Goetz's cases. In others, however, the electrocardiogram was grossly abnormal, the tracings ranging from bundle branch block to auricular fibrillation. In one of his patients all the heart beats were extrasystoles which originated from 8 different foci.

The intense cyanosis and orthopnea in these cases has had little attention. One case was classed as Ayerza's disease (black cardiac). Goetz believes that pulmonary vascular lesions plus thickening of the alveolar septa, compensatory emphysema and some degree of rigidity of the thorax due to involvement of the muscles, and the hemodynamic disturbances resulting from myocardial fibrosis adequately explain the cyanosis as being due to anoxia. In one case this explanation was supported by an increasing erythrocytosis and increasing hemoglobin in the blood as the disease progressed.

In one of Bevans' patients pericarditis was present and appeared to be both recent and old. According to Lewin and Heller,<sup>43</sup> pericarditis was present in 8 of 29 cases of scleroderma observed at necropsy. In some of these cases with other conditions associated (especially tuberculosis and rheumatism), the accompanying pericarditis cannot be definitely attributed to scleroderma. In Bevans' cases the lesion in the pericardium presented a hyalinization of collagenous tissue which was reconcilable with the lesions of scleroderma in other parts of the body. In her Case 1, the acute lesion overlying the chronic fibrous pericarditis was diffuse and too advanced to be included among those related changes which sometimes occur in

uremia. Since there were similar thickening and hyalinization of other serous membranes, particularly the peritoneum, it seemed justifiable to Bevans to include those in the pericardium as part of the disease, scleroderma, and not as manifestations of the uremic state.

*Endocrine Gland Involvement.* The volume of literature on this phase of the scleroderma question is so large and so controversial that a separate study and analysis of even a few years' production would be necessary for an adequate appraisal. Accordingly, in this general summary of the visceral manifestations of scleroderma only trends can be indicated. It is pertinent to call attention at this point to a few of the previous collections of data on the endocrines and scleroderma. It is necessary, however, to indicate that the views expressed are usually conjectural, contradictory and generally inconclusive as to the precise connection of the endocrine symptoms to scleroderma. The situation remains the same today. Castle<sup>9</sup> in 1923 and Boardman<sup>7</sup> in 1929 made extensive reviews of the literature which are worthy of study in the original. Other reviews are available by Seale,<sup>67</sup> and by Ehrmann and Brünauer<sup>16</sup> in Jadassohn's Handbuch. The best-established relationship between the endocrines and scleroderma is a disturbance in calcium metabolism. This will be discussed below. Thyroid symptoms in scleroderma have received much attention. Abnormal (high or low) basal metabolic rates have been observed (O'Leary and Nomland<sup>68</sup>) and thyroid medication has on occasion been beneficial. On the other hand, Haldin-Davis<sup>26</sup> was unable to find evidence of scleroderma in 100 patients with thyroid disease. Ovarian dysfunction too has been reported in scleroderma. The literature in this phase has been ably summarized

by Wiener<sup>51</sup> as follows: "Amenorrhea, dysmenorrhea, onset of the disease in pregnancy and in the spontaneous and induced menopause, findings of ovarian changes, the therapeutic success of estrogens, and the 3 to 1 predominance of the female sex are reasons enough to consider the gonads. The situation is similar with regard to the pancreas, thyroid and pituitary." Not always, however, is widespread endocrine gland involvement so clear-cut. One recent example will suffice. In her careful study of 2 patients, Bevans<sup>6</sup> found no definite lesions in the parathyroid glands (1 case), the pituitary glands, and the adrenal glands (2 cases). The thyroid gland in one case showed moderately increased fibrosis and proliferative lesions in the vessels; Case 2 showed more extensive involvement of the entire gland. Neither patient had shown clinical signs of thyroid dysfunction.

*Calcium Metabolism.* Disturbance of calcium metabolism is consistently found in scleroderma. This is especially prominent when scleroderma occurs together with calcinosis such as is the case in so-called Thibierge-Weissenbach syndrome. Since there is evidence that scleroderma may in some way be related to hyperfunction of the parathyroid gland and since the latter has a definite relationship to calcium metabolism, it is apparent that this may be the basis for the disturbed calcium metabolism. There is an extensive background in the literature for this concept. It has been reviewed in extenso by Cornbleet and Struck,<sup>10</sup> Goetz<sup>22</sup> and Basch.<sup>4</sup>

This calcinosis in the subcutaneous tissue in cases of scleroderma has been known since 1878 (Weber<sup>11</sup>). In 1910 Thibierge and Weissenbach<sup>12</sup> described a personal case and reviewed 8 others from the literature. Subsequently numerous authors described cases and in

1932 Basch<sup>4</sup> (a follower of Weissenbach's) in a comprehensive thesis collected as many as 46 cases from the literature. Since then, this syndrome has become known as the Thibierge-Weissenbach syndrome. It occurs almost exclusively in women, often suffering from ovarian hypofunction, and is preceded by or associated with vasomotor disturbances, parasthesias, acrocyanosis and angiospasm, and Reynaud's syndrome, especially of the upper extremities, resulting in sclerodactylia.

The calcinosis is regularly deposited and affects parts of the body subjected to pressure; that is, the tips and the volar surfaces of the fingers, the arms along the ulnar border, the elbows, the skin along the shin and in front of the patella and over the tuber ischii. This distribution suggests that trauma may be the *precipitating* cause.

Two types of calcinosis have been distinguished: (a) calcinosis circumscripta and (b) calcinosis universalis. In the former the calcium deposits are located in the subcutaneous tissue only but in the latter they also occur in the mesenchymal tissue as well. Calcinosis circumscripta occurs in the Thibierge-Weissenbach syndrome.

Goetz has ably analyzed the recent literature on this problem as follows: "Numerous theories have been advanced to explain the pathogenesis of calcinosis but 'in spite of the ever-increasing volume of literature on the subject one is confused by the increasing complexity of the theoretical considerations' (Brody and Bellin, 1937). It is natural that the calcium metabolism should have been incriminated and the literature on that subject has grown to a considerable volume. Those who are interested should consult the excellent article by Brooks (1934). Most authors found normal serum calcium and blood phosphorus levels and this could be confirmed in our

patient. However, as Bauer, Marble and Bennett (1931) put it, the serum calcium shows only the height of the stream and not its direction. Calcium balance studies are therefore essential in these cases. Only a few reports are available. Bauer *et al.* (1931), Paggi (1934), and Cornbleet and Struck (1937) reported a tendency to retain calcium and phosphorus following probably normal absorption. In all our cases the calcium balance was negative which is in agreement with reports by Dowling (1940) and Byron and Michalover (1943). In addition the serum phosphatase was normal and there was no decalcification of the bone.

"In this connection, it is the parathyroids which have been blamed more than any other agent on account of their known role in calcium metabolism and both scleroderma and calcinosis have been considered to be due to disturbances of these glands (Selye, 1932; Weissenbach *et al.*, 1933; Leriche, 1935; Leriche and Jung, 1935; and Kusunoki, 1939). Selye reported that following intraperitoneal injection of as little as 5 units of parathyroid extract, sclerodermatous lesions with calcific deposits in the skin developed in 20% of his rats. Following this concept, Leriche (1935) suggested parathyroidectomy and his good results were supported by some; other authors could not substantiate them (Dowling, 1940 and Byron and Michalover, 1943). Obviously hyper-parathyroidism could not account for all the clinico-pathological features of our case of scleroderma."

*Nervous System Manifestations of Scleroderma.* Although in the past a number of nervous system manifestations (central and peripheral) of scleroderma have been reported, these are certainly uncommon. Furthermore, their exact relationship to scleroderma is much less well established than the

associated lesions in some other organs. The same considerations apply to the later literature.

In Kanee's<sup>35</sup> case, Duryee, in personal communication, reported that electroencephalographic studies revealed a moderate degree of diffuse electrocortical activity. Duryee has found this in over 80% of cases of generalized scleroderma. Bevans stated that: "changes in the central nervous system were studied extensively by Dr. Abner Wolf and were not considered noteworthy in the present connection. Unfortunately the sympathetic ganglia were not studied. The sympathetic plexuses in the gastrointestinal tract showed no structural alteration. Whether lesions of the sympathetic system are responsible for the spasm exhibited roentgenologically in the gastrointestinal tract awaits investigation. To date, the results of sympathectomy for Raynaud's syndrome in patients who develop scleroderma have been variable and not encouraging."

Guss<sup>23</sup> reported in 1947 what he considered to be the second patient with scleroderma in whom convulsions occurred. From the facts and the author's own analysis, this patient's disorders really had a vascular rather than neurogenic origin. At any rate the precise sclerodermatous nature of the nervous system manifestations in this case is not evident.

*Skeletal Muscle Involvement.* Involvement of skeletal muscle in cases of scleroderma has been known for about 80 years. Since the first description of this lesion much work has been done to show that scleroderma and dermatomyositis are variations of one process (Nixon, 1907<sup>31</sup>; Langmead, 1923<sup>12</sup>; Dowling and Griffiths, 1939<sup>14</sup>; Lewis, 1940<sup>14</sup>; Dowling, 1940<sup>15</sup>; Freudenthal, 1940<sup>18</sup>; and Griffiths, 1940<sup>24</sup>) or are actually 2 different diseases (Weber and Gray, 1924<sup>7</sup>; Brock, 1934<sup>8</sup>;

Kinney and Maher, 1940<sup>37</sup>; Keil, 1940<sup>36</sup>; O'Leary and Waisman, 1940<sup>37</sup>; and Horn, 1940<sup>32</sup>) Brock, 1934,<sup>8</sup> in his review of the literature, noted that it is difficult to distinguish between scleroderma and dermatomyositis from histopathologic or clinical features during the early stages. But as induration and sclerosis advance, differences in the clinical picture as well as the histopathology become characteristic (Cf. O'Leary and Waisman). In scleroderma the inflammatory infiltrations at the later stage are minimal and perivascular cell infiltration is present in small foci only. The vessels become thick, their lumen narrow and often occluded followed by recanalization. There is proliferation of connective tissue fibres with subsequent sclerosis, hyalinization and calcareous degeneration. The muscle fibres undergo secondary degeneration which is in direct proportion to the degree of sclerosis.

In dermatomyositis, Brock<sup>8</sup> finds that the diffuse infiltration of lymphocytes and plasma cells in the cutaneous, subcutaneous and the muscular tissue remain the outstanding feature to the end. Perivascular infiltration is another prominent feature. The degeneration of the muscle fibres is marked and dependent on the inflammatory process. The changes in the vascular and connective tissue are minimal.

The difficulty of really distinguishing between the 2 processes is emphasized by Goetz's patient in which the findings suggest that he was dealing with a type of case which forms a connecting link between scleroderma and dermatomyositis.

*Bones and Joints.* The involvement of bones and joints by the sclerodermatous process is so well known and accepted that little new has been added to our knowledge recently. Jackman<sup>32</sup> in his study of the roentgen features of scleroderma and acrosclerosis in 4

cases noted that although the most striking feature is calcinosis usually involving pressure points on the skin, another finding is the slow progressive absorption of the distal phalanges of the fingers. This occurs more often in acrosclerosis and does not become marked until the disease has been present for years. Terminal absorption may be associated with calcinosis and occasionally with increased intraosseous deposition of calcium. Synostosis between the distal and middle phalanges may occur.

*Eye.* Although cataracts have been reported occurring with scleroderma, it might be stated in passing that Werner's syndrome (progeria in the adult), a heredofamilial disorder with scleroderma, bilateral juvenile cataract, precocious graying of the hair and endocrine stigmatization so well described by Oppenheimer and Kugel in 1934 and 1941<sup>59</sup> should not be properly included in this discussion on scleroderma in spite of the many manifestations of this process also associated with scleroderma. Thannhauser<sup>70</sup> in an extended study in 1945, showed that the title scleroderma with cataracts is misleading and that the cutaneous changes in this anomaly are not those of true scleroderma. The same can be said of Rothmund's syndrome, a process in which cataracts are associated with a peculiar degeneration of the skin. Thannhauser proposes that the cutaneous lesions of Werner's syndrome be called "heredofamilial atrophic dermatosis with skin ulcers," and that of Rothmund's syndrome "heredofamilial atrophic dermatosis with telangiectases."

*Miscellaneous Involvement.* Abnormalities in other structures have been found in a small number of cases. It is open to serious question whether these effects are sclerodermatous or merely coincidental findings. Among

the organs involved are the kidneys, the teeth and gums, the uterus, and the prostate. Bevans, for example, found extensive renal lesions in both of her cases. The medium sized and smaller arteries were especially involved. The glomerular lesions were similar to those found in lupus erythematosus. Tubular alterations were severe, and the renal pillars were thickened. The larger vessels in the peripelvic fat showed the same type of perivascular fibrosis as that observed in other parts of the body. The pathologic findings were far in excess of the clinical and laboratory data indicating renal disease. Although uterine atrophy had been noted by others, no such change was observed by Bevans in her first case. However, the lamina propria of the vagina and external cervical os shared in the generalized connective tissue thickening that occurred in the skin and elsewhere. The ovaries appeared to be normal. The smooth muscle in the prostate of Case 2 appeared to be atrophic and could, according to Bevans, represent sclerodermatous rather than involutional change.

Retraction of the gingival margins with loosening of the teeth have been noted in the older literature of scleroderma. Davis and Saunders (1946)<sup>11</sup> have recently presented a case of scleroderma involving the face and gingiva. In a careful study Stafne and Austin<sup>69</sup> observed radiographically a characteristic dental abnormality in acrosclerosis and scleroderma. It is an increase in the width of the peridental space, which, when it does occur, is sufficiently characteristic to cause the presence of acrosclerosis to come to mind. Among 127 cases of acrosclerosis and scleroderma at the Mayo Clinic, 9 (7.08%) had this anomaly. It occurred in 4 men and 5 women of 36.9 years average age. Eight of the patients had acrosclerosis and 1 had

scleroderma. While all the teeth may be affected, the posterior are involved more than the anterior. Microscopical examination of 1 specimen showed that the increased periodontal space is occupied by markedly thickened periodontal membrane. The thickening of the vessel walls suggests to the authors that the change in this membrane is probably produced by the circulatory disturbance which is a salient feature in acrosclerosis and diffuse scleroderma. Sometimes certain cases of scleroderma are complicated by other diseases which, while unrelated, may improve under therapy for the scleroderma. Kusunoki and Kuwabara<sup>41</sup> reported a case of diffuse scleroderma accompanied by leukemia which improved following parathyroidectomy. While this suggests the probable value of blood studies in scleroderma, the therapy can by no means be considered applicable to the general therapy of leukemia.

Because it summarizes the present-day status of scleroderma so well and so succinctly, we quote the conclusion of Goetz's comprehensive survey of the visceral manifestations of scleroderma: "Obviously the term 'scleroderma' should be abandoned. It is quite evident today that we are dealing with a systemic disease neither solely nor primarily involving the skin. 'Scleroderma' is only the obvious and striking symptom of a generalized disease and the most serious symptoms actually arise in the viscera.

"Now that the visceral changes are being more widely recognized as an

integral part of the disease, the systemic implications will receive much more consideration than the dermatological aspect. Physicians will be more on the look-out for these changes and undoubtedly more reports will appear in the literature. It appears therefore to the writer that now is not an inopportune time to abandon the term 'scleroderma' which for so long has obstructed investigation into the cause of that disease and to replace it by one more descriptive of the true state of affairs. The term 'sclerosis' already being in use, it appears that '*Progressive systemic sclerosis*' would describe the condition adequately until such time as the etiology has been established. Scleroderma is then only one of the symptoms or signs of progressive systemic sclerosis.

"Progressive systemic sclerosis may be defined as an induration and sclerosis which may occur in any organ inclusive of the skin, the muscles and the blood vessels. Pigmentation, loss of weight, asthenia, arthritis and other symptoms occur, depending on the degree and extent of the sclerosis. Everywhere the same changes occur, viz., edema, followed by proliferation of connective tissue and sclerosis of collagenous bundles, resulting in many cases in atrophy of the organ concerned. This may occur in the connective tissue of the skin, in the interstitial tissue between the alveoli of the lungs, the acini of the liver, in the kidney, the muscle fibres of the heart, within the pulp of the spleen and in the endocrine glands."

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# OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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## A PSYCHOSOMATIC APPROACH TO VASOMOTOR RHINITIS

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For many years vasomotor rhinitis has been recognized as a disorder in which emotional factors may play an etiological role. Some textbooks of otolaryngology include "psychic disturbances" in a list of possible causes and mention two old synonyms, "intermittent neurotic catarrh" and "nervous coryza." Almost nothing is said, however, about what the emotional problems are or how they exert their effect.

On the basis of clinical and experimental studies it appears that psychogenic factors may play a part in at least 3 ways: 1) the result of fear or anxiety, 2) the result of a conflict and 3) the result of direct suggestion. These mechanisms will be discussed in some detail and then considered in their interrelationships to other etiological factors.

For the purpose of this discussion, Lederer's<sup>1</sup> definition of vasomotor rhinitis will be used. He defines the entity as "a condition characterized by intermittent engorgement of the nasal mucosa, sneezing associated with a free flow of diluted mucus and nasal obstruction." There have been efforts to sub-type cases on etiological and pathological grounds and it seems likely that a number of dissimilar processes are grouped under a single heading.

The first pattern in which emotional factors play a causative part occurs as

a reaction to impending danger. In response to fear there is an initial vasoconstriction which is followed by a vasodilatation. This is comparable to the local effect of epinephrine. The clinical picture in the "after-phase" is that of vasomotor rhinitis.

Vasoconstriction within the nose in response to fear is part of a general homeostatic adaptation which prepares the organism for fight or flight. According to Post,<sup>7</sup> when the body is alerted for action, changes occur which prepare the nose to accommodate an increased oxygen intake. The airway is enlarged and a greater mucus production is provided to moisten the added air volume. To accomplish the former the size of the turbinates is altered by the smooth muscle tissue distributed about arterial and venous tracts and in the walls of the spaces of erectile tissue. These structures are innervated by sympathetic fibers.

Post's<sup>7</sup> observations have added to our knowledge of the effect of fear on the nose. Studying a group of returning combat men who continued to react as though they were in dangerous situations, he noted a vasoconstriction within the nose. The after-phase response was that of blockage due to a relaxation and turgescence of the erectile tissue within the turbinates. In other words, the veterans continued

to react as though they were facing a threatening situation even though they were safely back in the United States.

It is important to realize, further, that the clinical picture of vasomotor rhinitis may be produced by any unconscious, internal conflict which gives rise to anxiety, just as it is produced by an external danger or recent and repeated exposure to situations which give rise to fear. A "forbidden" wish which threatens to erupt into consciousness and to create conflict will stir up anxiety which results in a reaction that parallels the response to a terrifying experience. In both instances the effect follows sympathetic nervous system stimulation and is only one in a series of tension responses.

A second pattern in which emotional factors are important has been described by Wolff *et al.*<sup>11</sup> In their group of experimental subjects, changes were observed in the nose after unsympathetic discussion of pertinent and conflictual problems. These changes consisted of an "initial hyperemia associated with turgescence of the erectile tissue in the turbinates, . . . engorgement of the nasal mucosa and increased secretion. Often after the subsidence of hyperemia, secondary pallor ensued with the mucous membranes of the nose remaining boggy and edematous." The authors believed that the impulses which effected the changes were carried by the vagus nerve. The primary picture was principally that of vasodilatation while the secondary one was that of edema.

A case reported by Fowler<sup>3</sup> points to the conclusion that an autonomic imbalance with a preponderance of parasympathetic (or a decrease in sympathetic) activity results in the clinical picture of vasomotor rhinitis. In his patient a unilateral disturbance developed on the side on which the stel-

late (sympathetic) ganglion was removed.

According to Proetz<sup>8</sup> the autonomic nervous system "functions below the level of consciousness, is not subject to the control of the will and serves to carry on the purely vegetative processes, such as vascular tone, the action of smooth muscle fibers and the regulation of glandular secretion. It therefore enters largely into the emotional states . . ." Essentially the autonomic nervous system may serve as an outlet for energy which is not released in words, thoughts or action because of conflict and repression. The impulses thus conveyed to the nasal structures give rise to a disturbance in function.

Wolff *et al.*<sup>11</sup> do not describe the nature of the conflict or conflicts which they activate. It would be important to determine whether or not there is a specific conflict which gives rise to the changes they observed. Studies<sup>9</sup> have made it clear that a particular conflict expressing itself via the vagus nerve plays an important part in the etiology of peptic ulcer. Might not this be so, also, in certain cases of vasomotor rhinitis?

While the first two patterns involve the autonomic nervous system as a pathway, the third is the result of direct suggestion. The experiment of using an artificial rose to induce an "allergic attack" is an old one, and it has been repeated a number of times. During the attack the nasal mucous membrane will become edematous and pale gray. Within a few minutes of the time that the patient sees that the flower is only paper, the symptoms and the congestion subside. Metzger,<sup>5</sup> an allergist, recently performed this experiment with a paper goldenrod in the month of June.

The response to medication in some cases of vasomotor rhinitis also illustrates the effect of direct suggestion.

In the Asthma Research Council's Report of Progress (1938),<sup>1</sup> it was stated that the results of treatment with a placebo (saline solution) were slightly better than those obtained by protein desensitization. Although the series was small (32 and 35 patients), the study called attention to the influence of suggestion.

For many years it has been known that symptoms can be induced, reproduced and removed by direct suggestion. Charcot demonstrated this fact with the aid of hypnosis. An "allergic attack" precipitated by an artificial flower is such a symptom.

Among the factors which play an etiological role in vasomotor rhinitis are emotional, endocrine, allergic, thermal and constitutional. In certain instances one component predominates while in other cases it is another. Only rough measurements are possible since the nasal dysfunction involves a complex interrelationship of a number of known and perhaps several unknown factors.

Explanations for the interaction of all the various etiological forces have not been worked out, but two theories have been advanced by Urbach<sup>10</sup> to explain the connection between the psychogenic and allergic components. "Perhaps the best explanation is that such influences (emotional) bring an alteration in the excitability of the autonomic nervous system and that stimuli until then of the sub-threshold level thus acquire the capacity of acting as excitants. Another possibility is that psychic stimuli, by their effect on the vascular innervation, bring about a change in the blood supply of the peripheral tissue. The result is that pathologic substances that normally cannot penetrate the vessel walls are now absorbed, leading to an antigen-antibody reaction."

The influence of endocrine changes has received some attention. There are

clinicians who believe that a thyroid deficiency is important. According to Proetz,<sup>8</sup> "circulatory changes evidenced chiefly by pallor are to be found in the nasal mucosa in the presence of thyroid insufficiency." Mohun<sup>6</sup> reports that hyperemia and edema of the nasal mucous membrane may develop late in pregnancy in patients who never had symptoms before and that the disturbance is often aggravated in those who had previous trouble. He maintains that there is a definite tendency toward hyperemia and edema when the estrogen level is high. One would suspect that a combination of endocrine and emotional factors operate during pregnancy and that the emotional factors center around conflictual feelings about pregnancy and motherhood.

Although infections may play an etiological role in vasomotor rhinitis, it is probably more common for them to appear as complications. The nasal dysfunction opens the road to bacterial invasion. Fabricant<sup>2</sup> has found that in susceptible persons emotional states "can produce transient conversions of nasal secretions from a normal, slightly acid to an abnormal alkaline state." There is evidence that acidity is unfavorable to the growth of pathogenic bacteria, while alkalinity favors their growth. A shift in the pH of the nose to the alkaline side accompanying vasomotor changes is no doubt one in a group of factors responsible for bacterial invasion.

Sinusitis occurs secondarily and is the result of changes within the sinus lining membrane, direct extension of infection and interference with normal drainage. Other complications may be otitis media and laryngitis. There are emotional sequelae as well. Anorexia, weight loss, insomnia and impairment of efficiency may accompany a prolonged attack. The fatigue in turn aggravates the initial process.

If there are recurrent and prolonged attacks of vasomotor rhinitis irreversible morphological changes are to be anticipated. There will be hyperplasia and later hypertrophy of the surface epithelium. In certain areas the cilia will disappear. The ducts and acini of the mucus glands in the subepithelial layer will be filled with and dilated by secretions. Degeneration into cysts will occur. As the lesion progresses, atrophic changes will be seen and the mucus glands may disappear.

From this discussion it is evident that vasomotor rhinitis is a dynamic process. The picture presented at any particular moment depends upon the interaction of a number of forces and the intensity and duration of the physio-pathological changes. As in any process in motion there will be shifts in the weight of the various etiological factors from time to

time. Initially the sensitivity to an inhalant may occupy the center of the stage. Later emotional conflicts may express themselves through this "ready-made" avenue. Innumerable combinations are possible.

It is important to consider vasomotor rhinitis in terms of the total organism. A description of the physiological or pathological state is not enough. Attempts should be made to understand the process on the basis of the various etiological factors that play a part. Emotional influences should not be neglected. Three primary modes of operation have been considered in this article. These mechanisms are not mutually exclusive. They must be viewed in terms of their relationship to one another and in terms of their interaction with other causative agents.

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# BOOK REVIEWS AND NOTICES

**THE MECHANISM OF ABDOMINAL PAIN.** By V. J. KINSELLA, M.B., Ch.M. (Syd.), F.R.C.S. (Eng.), F.R.A.C.S. Pp. 230; 17 figs; 8 plates. Sydney, Australia: Angus & Robertson. Price 32/6.

THE significance of pain of abdominal origin has long been recognized. The interpretation of such pain, however, has been rendered difficult by the conflicting concepts of the mechanisms involved.

The author has given consideration to those accepted concepts of the past, which in general deny the existence of true and direct visceral pain. The erroneous conclusions reached in the past with respect to the existence or non-existence of true visceral pain are due, in the opinion of the author, to the inherent difficulties attendant upon animal experiments in this field. By experiment and observation on human subjects under local anesthesia the author has convincingly demonstrated the sensitivity of diseased viscera without implication of the mesentery and parietal peritoneum. He admits that the mesentery and parietal peritoneum are highly sensitive and frequently contribute to the severity of the abdominal pain of visceral origin, but believes that these structures need not be stimulated to evoke a painful sensation from diseased viscera.

The author further believes that the effective stimulus for pain, both somatic and visceral, is increased tension within the tissues, be that the result of inflammation or muscular contraction.

The concentration of nervous elements within the viscus is low, while the concentration of such elements is relatively high in the mesentery especially along the vessels. The mesenteric border of any given viscus is, therefore, more sensitive than the antimesenteric side. If 1 sq. cm. of mesentery should be crushed, the number of painful stimuli elicited is considerably higher than if 1 sq. cm. of the viscus itself is crushed. Thus, it is that mesenteric pain is said to be of a high order while that of the viscus is relatively low. A narrow segment of bowel may be crushed with a clamp without eliciting a painful response, but if a wider segment is similarly crushed painful stimuli are elicited.

Some attention is directed to the pain associated with some of the commoner clinical disorders, and an attempt is made to explain this upon the basis of pure visceral sensitivity.

The book should prove of special interest to the surgeon.

I. R.

(480)

**INTRACRANIAL TUMORS.** By PERCIVAL BAILEY, Prof. of Neurology and Neurologic Surgery, Univ. of Illinois. 2d ed. Pp. 478; 16 plates; 155 figs. Springfield, Ill.: Charles C Thomas, 1948. Price, \$10.50.

THIS book combines to an excellent degree neuropathology, neurology and neurosurgery. Both student and the senior neurosurgeon will be well advised to consult it. The parts on neuropathology, as is to be expected from this author, cover all demands. The illustrations are adequate, the pen and ink drawings of the microscopic fields showing cell detail surprisingly well. The drawings of the gross specimens of tumors *in situ* are less effective. The weakest section deals with the surgery of brain tumors. Constant reference is made to methods formerly used in the Brigham Hospital and there have been neurosurgical advances since 1930, few of which are recorded. But, as the author states in his preface, this book has been written for students who need not be too greatly interested in operative detail. If they take up neurosurgery and find themselves in a modern clinic, their conception of neurosurgical technique can be properly learned by first-hand experience.

F. G.

**ROENTGEN STUDIES OF THE LUNGS AND HEART.** By NILS WESTERMARK, M.D., Caroline Institute, University of Stockholm, Sweden. Pp. 216; 98 ills. Minneapolis: Univ. of Minnesota Press, 1948. Price, \$7.00.

THIS excellent monograph contains a series of guest lectures given by an eminent Swedish radiologist at Minneapolis. The approach is primarily through application of principles of physiology and the alterations in them occurring in disease. This point of view is indicative of the new attitude toward roentgen investigations as a whole but particularly as it is directed toward the chest. The stimulating observations are profusely illustrated and documented and represent a very rich experience during 20 years' practice in a teaching institution. Perhaps the most interesting and provocative chapters deal with the importance of the intra-alveolar pressure in the diagnosis of pulmonary diseases and the roentgen diagnosis of pulmonary embolism.

The American physician may encounter some difficulty in accepting some of Dr. Westermark's statements in regard to pulmonary

physiology and it must be admitted that a few of the important points which are made in the text cannot be easily seen on the illustrations. In spite of the unfamiliar method of thinking which the reader may encounter, or possibly because of it, this little book will make a graceful addition to the library of all who are interested in the chest, its function and diseases.

R. B.

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**MEDICAL HYPNOSIS.** By LEWIS R. WOLBERG, M.D., Asst. Clinical Prof. of Psychiatry, New York Medical College. 2 vols. Pp. 439 and 513. New York: Grune & Stratton, 1948. Price, \$5.50 and \$6.50.

THIS is a comprehensive work by a man well qualified to write on the subject. Psychoanalytically trained, he was taught the technique of induction of hypnosis by Dr. M. H. Erickson.

A summary of the contents is presented in the preface: "A considerable portion of Volume I is devoted to a step-by-step description of the induction process, illustrating various induction methods by excerpts from transcriptions of actual hypnotic sessions. There is a didactic discussion of the principles of psychotherapy, and of the psychopathologic factors in the different disease syndromes. Therapeutic methods . . . are elaborated on in some detail. . . . Volume II contains 3 complete transcribed case histories which enable the reader to . . . observe the therapeutic management of the patient . . . as these illustrate a preceding discussion of the uses and limitations of the chief short-term psychotherapeutic methods."

The 2 volumes contain a wealth of information which will be of interest to everyone who is concerned with psychotherapy in general and with the employment of hypnosis in particular. The detailed recordings of case histories are especially worth noting. Numerous references to the literature on hypnosis are included.

W. P.

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**VASCULAR DISEASES IN CLINICAL PRACTICE.** By IRVING SHERWOOD WRIGHT, M.D., Assoc. Prof. of Clinical Medicine, Cornell Univ. Medical College. Pp. 514; 104 ills. Chicago: Year Book Publishers, 1948. Price, \$7.50.

THIS work presents the clinical aspects of diseases of the arteries, veins and lymphatics in a clear and concise manner. About half the book is devoted to diseases of the arteries, one-seventh to the veins and the rest to miscellaneous vascular conditions. The chapter on Methods of Study of the Patient is par-

ticularly well done. The chapter on the Hyperabduction Syndrome, based on the author's work, is instructive. The author's opinion concerning the merits of various forms of therapy is particularly valuable, in view of his large clinical experience.

The book is a valuable addition to the literature on vascular diseases, not only to the practitioner and internist, but also to those who make these diseases their major interest.

M. N.

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**BACTERIAL AND VIRUS DISEASES.** By H. J. PARISH, M.D., Clinical Research Director, Wellcome Foundation. Pp. 168; 14 ills. Balt.: Williams & Wilkins, 1948. Price, \$2.75.

AS THE subtitle (Antisera, Toxocils, Vaccines and Tuberculin in Prophylaxis and Treatment) indicates, this useful little handbook deals with the theoretical concepts of immunity, methods of preparation and standardization of therapeutic antisera and biologic preparations, methods of diagnosing susceptibility, and specific instructions as to serologic treatment of bacterial and viral diseases. At the end of the volume is a short historical sketch of developments in this field. As the author indicates in the preface, the book is designed to aid the busy practitioner in a better understanding of the principles underlying the prevention and treatment of infectious diseases. For American practitioners, however, it should be pointed out that dosages and the standardization of biologic preparations are based upon current British usage, which differs in some cases from those employed in the United States.

R. N.

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**RACIAL VARIATIONS IN IMMUNITY TO SYPHILIS.** By CHESTER NORTH FRAZIER, M.D., Sr.P.H., and LI HUNG-CHIUNG, M.D. Pp. 122. Chicago: University of Chicago Press, 1948. Price, \$2.50.

THIS monograph is the first comprehensive and scientific presentation of the actual differences in the reaction to syphilitic infection among Chinese, Europeans and Americans. The authors have demonstrated the patterns of syphilis by the elective localization in tissues and organs of Chinese population as compared with American White and Negro races, a reasonable comparison from the medical, geographic and other viewpoints. In the people of the 3 races they have analyzed 16-845 consecutive cases of syphilis, extending over a period of 10 years, July 1, 1927, to June 30, 1937. They found that "regardless of race or sex, the disease was essentially the



same in all people. Differences between races lay almost entirely in the relation frequency with which the phenomena of the disease developed. People of all three races had lesions of the skin and bones, of the brain and spinal cord, and of the heart and blood vessels." In spite of this similarity of pattern of syphilis in the 3 races, the authors found that in several important respects the disease was a less serious matter in the Chinese than in either the Whites or Negroes. The basis and probable mechanisms of this concept are outlined in detail.

Written by two competent authorities, this volume is interesting, well-composed, and attractively presented. The results will go a long way in helping to differentiate the effects of *Treponema pallidum* on an organism from the influence of moral and other factors which may be responsible for the so-called "immunity" enjoyed by certain races.

In the treatment of the literature, it would have been worth while to mention the efforts of other workers who have attempted better definition of the manifestations of syphilis as they occur in the American Negro at least, particularly Hazen. Otherwise, this is a praiseworthy handling of an important problem of syphilology. H. B.

**CLINICAL OPHTHALMOLOGY.** By H. M. TRAQUAH, M.D., Consulting Ophthalmic Surgeon, Royal Infirmary, Edinburgh. Pp. 264; 72 ills., 8 in color. St. Louis: C. V. Mosby, 1948. Price, \$9.00.

THE author states in his preface that the book might be called "Ophthalmology without an ophthalmoscope." The omission of examination of the fundus with the ophthalmoscope the reviewer feels is a mistake. In the teaching of medicine in the medical schools of the United States, the student is becoming instructed more and more in the use of the ophthalmoscope. There is no reason why a general practitioner should not be able to make an examination of the fundus adequate to detect gross changes, such as hemorrhages and exudates and the general condition of the retinal blood vessels. If the use of the instrument is begun early, the physician will become sufficiently adept with it to enable him to tell whether or not the fundus is normal, and if not to refer the patient to someone who is more expert.

Apart from this defect, the book is excellent. The external diseases are well described and illustrated and there is much of practical value to be found. It can be recommended to every general physician as a working text for all ophthalmic conditions except those relating to the fundus oculi. F. A.

#### SURGICAL TREATMENT OF THE ABDOMEN.

Edited by FREDERIC W. BANCROFT, M.D., F.A.C.S., Prof. of Clinical Surgery, New York Medical College, and PRESTON A. WADE, M.D., F.A.C.S. Pp. 1026; 457 ills.; 3 color plates. Phila.: J. B. Lippincott, 1947. Price, \$18.00.

THIS is an enlarged, completely revised edition of an earlier work published by Appleton-Century under the title of "Operative Surgery". Thirty-six eminent contributors have provided excellent discussions of the surgical treatment of disorders of the alimentary tract, biliary tract, liver, pancreas, and spleen. In addition to surgical techniques, and pre- and postoperative care, there are included sections on blood transfusions, anesthesia and fundamental principles of surgical technique. No attempt is made to discuss symptomatology or differential diagnosis. The up to date and authoritative discussions deal with treatment or treatments of a given lesion. This book should be available to all who are interested in abdominal surgery. H. Z.

#### RECENT PROGRESS IN HORMONE RESEARCH.

Edited by GREGORY PINCUS. Proceedings of the Laurentian Hormone Conference. Vol. II. Pp. 427; illustrated. New York: Academic Press, 1948. Price, \$8.00.

THESE papers, dealing with highly specialized aspects of endocrinology by those who are doing research in the field, are grouped under 5 headings: 1. physical methods in hormone research; 2. pituitary control and activity; 3. hormone metabolism; 4. hormonal regulation of metabolism; 5. aspects of clinical endocrinology.

Many charts and figures illustrate the data presented and most of the papers are presented in an admirable manner. Following each paper there is reported the informal discussion of those participating in the conference and this adds a great deal to the interest of the volume. Use of the data is facilitated by an index.

In the matter dealing with clinical aspects, the Reviewer deplores the procedure of determining human sperm counts, accomplished by methods which moralists condemn as immoral misuse of the sexual function. In the discussions of the administration of male sex hormones to patients there seems to be a concentration of interest on the physical effects resulting, without advice of avoiding overstimulation with its associated psychological effects. I. Z.

## NEW BOOKS

*Conference on Liver Injury.* Transactions of the Fifth Meeting. Pp. 127; 30 ills. *Liver Injury.* Transactions of the Sixth Conference. Pp. 74; 9 ills. New York: Josiah Macy, Jr., Foundation, Sept. 26-27, 1946; May 1-2, 1947. Price, \$2.25 and \$2.00.

For some years past the Josiah Macy, Jr., Foundation has sponsored conferences on liver injury. The conferences are round-table discussions of subjects of interest to clinicians and investigators of liver injury in the broadest sense. The 5th and 6th Conferences deal with such important subjects as the relation of dietary factors to chemical injury, impairment from vitamin deficiency, liver function studies, chronic hepatitis, therapy in liver diseases, cirrhosis, the hepatorenal syndrome, chromatography in the study of liver diseases, and massive hepatic necrosis. Each subject is briefly presented and the resulting discussion summarized.

The Conferences on Liver Injury are valuable, and afford an excellent survey of present day investigations in the liver field.  
B. L.

*Agonal Acidosis.* By IB FABRICIUS-HANSEN, Oresunds Hospital. Translated by HANS ANDERSEN, M.M. Pp. 134. Copenhagen: Povl Branner; New York: Stechert-Hafner, 1948. Price not given.

This monograph is a report of a detailed study just antecedent to death of the acid-base and electrolyte balance in a series of cases. The monograph contains discussion and experimental data of interest to the specialist in this field.  
W. S.

*Handbook of Ophthalmology.* By F. E. L. GOAR, M.D., F.R.C.S. (Ed.), Baylor Univ. College of Medicine. Pp. 166; 48 ills, 7 color plates. St. Louis: C. V. Mosby, 1948. Price, \$5.50.

This book is the outcome of a series of lectures delivered to medical students. The author has made an attempt to condense the knowledge a medical student and a general practitioner should have of ophthalmology. The selection of the material he has made will be criticized or applauded, depending upon what the reader thinks is important. Obviously there will be no unanimity of opinion. The book will probably serve its purpose as an introduction to ophthalmology, but can hardly be regarded as a serious text for the general practitioner. It can be recommended only as a primer.  
F. A.

*The Psychological Origin and Treatment of Enuresis.* By STEVENSON SMITH, Ph.D. Pp. 70. Seattle: University of Washington Press, 1948. Price, \$1.75.

This little book offers a concise discussion of the psychology of enuresis. The material is "down to earth" yet on the whole the ideas expressed are acceptable to even advanced students of child behavior. It should constitute a valuable aid to physicians and parents who cope with the problem of bed-wetting. It is concise, humorous and very helpful.  
V. H.

*20th Century Speech and Voice Correction.* Edited by EMIL FROESCHELS, M.D. 19 contributors. Pp. 321; 33 ills. New York: Philosophical Library, 1948. Price, \$6.00.

THOUGH differing occasionally, these contributors have given us a helpful book. Of the 22 chapters, Dyslalia is accorded most space; this includes all functional defects of articulation, common causes being deafness, inactivity of muscles of articulation, mental deficiency, hyperemotionality, and injuries to various oral parts. Prosthetic Therapy of the Cleft Palate is a well illustrated chapter.  
N. Y.

*Medical Clinics of North America. Symposium on Psychiatry and Neurology.* New York Number. Pp. 558-853. Phila.: W. B. Saunders, May, 1948. Price, \$16 a year.

THE editor points out that the material covers a wide field in the ever expanding domain of psychiatry and neurology. Many of the articles are probably much too technical for those outside the specialty. If this "Symposium" is for the benefit of the general practitioner it would seem that a much more satisfactory choice of articles could have been made.

Among the most valuable papers are: Headache, An Outline for Diagnosis and Treatment; Anxiety States, Their Recognition and Management; Differential Diagnosis of Coma. On the other hand there are those that are either exceedingly technical (i. e., "Hypnotic Psychotherapy"), or else founded upon principles which are controversial (e. g., "Electroshock Therapy in an Out-patient Setting"). Some of the psychodynamics put forward are open to question (e. g., "Alcoholism, Its Nature and Treatment"). Any symposium of this type for the general practitioner should contain only material which is generally accepted by the specialists in the field and should avoid articles of too technical nature.

D. A.

## NEW EDITIONS

**A TEXTBOOK OF GYNECOLOGY.** By EMIL NOVAK, M.D., F.A.C.S., Ass't Prof. of Gynecology, Johns Hopkins Medical School. 3d ed. Pp. 742; 484 ills. Balt.: Williams & Wilkins, 1948. Price, \$8.00.

IN THIS edition, the author has just about covered the non-operative portion of gynecology. In the discussion of sterility no mention is made of the work by Farris upon the timing of ovulation. Only one page is devoted to the subject of the anatomy of the pelvic floor.

The book is written through the eyes of a combined clinician, endocrinologist and pathologist and every page reflects the importance of each of these fields in the teaching and the practice of modern gynecology. The writing is so facile that the reading is effortless. Many of the illustrations are in color and both the microscopic and the gross pictures are purposeful and lucid. The chapters upon functional gynecological disturbances and upon *bachache* are especially replete with valuable information and sound advice.

As one reviews the book as a whole, the impression arises that it will be more readily assimilated by and therefore more valuable to the general practitioner and the younger specialist than to the undergraduate student.

F. P.

**LABORATORY DIAGNOSIS OF PROTOZOAN DISEASES.** By CHARLES FRANKLIN CRAIG, M.D., Emeritus Prof. of Tropical Medicine, Tulane Univ. Medical School. 2d ed. Pp. 384; 56 ills., 7 color plates. Phila.: Lea & Febiger, 1948. Price, \$6.50.

THE new edition of this book has been enlarged by 35 pages. Plates in color of the plasmodia of malaria and a number of newer diagnostic methods have been added. It would have been improved further had the author dropped some of the out-moded methods and been more critical of those which are included and more explicit in his statements of their value and the conditions under which they may be used.

H. R.

**DISEASES OF THE CHEST.** By ROBERT COOPE, M.D., B.Sc., F.R.C.P., Hon. Physician, Royal Liverpool United Hospital. 2d ed. Pp. 541; 163 ills., 8 in color. Edinburgh and Balt.: Williams & Wilkins, 1948. Price, \$7.50.

THIS book is designed for "students and practitioners". The first 6 chapters are devoted to the physiological and anatomical principles underlying diseases of the lung, with emphasis upon the segmental divisions of the lung lobes, and to the fundamental principles of physical diagnosis.

The main portion of the text is devoted to descriptions of the various acute and chronic lung diseases. The more common conditions are covered fairly completely; the rarer conditions receive at least a few paragraphs, to aid in the differential diagnosis. Diseases of the pleura and mediastinum are also covered, and there are chapters on chest injuries, oxygen therapy, and disturbances of the pulmonary circulation. The use of sulfonamides in pulmonary infections is discussed, but little space is given to penicillin, and streptomycin is not mentioned; this is undoubtedly due to the scarcity of those drugs in Great Britain.

The book is very well written, and contains numerous drawings to illustrate important points of the text. There is only one plate—an x-ray of a normal chest—in the main portion of the book; an appendix contains reproductions of 32 illustrative films.

This is not a reference book on pulmonary diseases, but can be recommended for general use to students and general practitioners.

H. H.

**A Handbook for Dissectors.** By J. C. BOILEAU GRANT, Prof. and Director, and H. A. GATES, Prof. of Anatomy, Univ. of Toronto. 3d ed. Pp. 415; 19 figs. Balt.: Williams & Wilkins, 1948. Price, \$3.00.

THIS is a dissecting guide for use in conjunction with a *Method of Anatomy*, the textbook by Dr. Grant. It is in no sense a textbook of anatomy and can not be used alone. Its value is limited mainly to the beginning student in the dissecting laboratory.

W. W.

**Midwifery.** By Ten Teachers, Directed by CLIFFORD WHITE, M.D., F.R.C.S. (Eng.). 8th ed. Pp. 560; 217 figs. Balt.: Williams & Wilkins, 1948. Price, \$6.00.

**Essentials of College Chemistry.** By C. H. WHITEFORD, Ph.D., and R. G. COFFIN, M.S. 3d ed. Pp. 632; 76 figs. St. Louis, C. V. Mosby, 1948. Price, \$4.75.

**Recent Advances in Obstetrics and Gynecology.** By ALECK W. BOURNE, M.A., M.B., F.R.C.S. (Eng.), and LESLIE H. WILLIAMS, M.D., M.S., F.R.C.S. (Eng.). 7th ed. Pp. 326; 85 ills. Phila.: Blakiston, 1948. Price, \$6.00.

**Clinical Laboratory Methods and Diagnosis.** By R. B. H. GRADWOHL, M.D., D.Sc., F.R.S.T.M. & H. (London). 3 Vols. 4th ed. Pp. 3300; 1100 ills., 56 color plates. St. Louis: C. V. Mosby, 1948. Price, \$40.00.

**Outline of Physiology.** By WILLIAM R. AMBERSON, Ph.D., and DIETRICH C. SMITH, Ph.D. 2d ed. Pp. 502; 192 figs. Balt.: Williams & Wilkins, 1948. Price, \$5.00.

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## ORIGINAL ARTICLES

### MASSIVE HYPERTROPHY OF THE HEART WITH SPECIAL REFERENCE TO BERNHEIM'S SYNDROME

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Massive hypertrophy of the heart provides interesting material for the study of the etiology of enlargement and the pathogenesis of cardiac failure in advanced heart disease. In his monograph, published in 1926, Cabot<sup>3</sup> pointed out the relationship of etiology to heart size. The concepts of left and right ventricular failure had been realized for many years prior to that, however. As early as 1728 Lancisi<sup>6</sup> described the consequences of right-sided failure, and later, in 1832, Hope<sup>5</sup> published his ideas on the symptomatology of left ventricular failure. The facts that both chambers may fail simultaneously and that failure is usually preceded by hypertrophy are also accepted axioms of cardiology.

In 1910 Bernheim<sup>1</sup> suggested an exception to the rule that the signs of right ventricular failure follow hypertrophy of the right myocardium, and in 1915<sup>2</sup> he amplified his thoughts on the matter. He believed that the syndrome of right ventricular failure without significant hypertrophy which bears his name resulted from eccentric left

ventricular hypertrophy or preponderant left ventricular hypertrophy of marked degree associated with minimal hypertrophic change of the right ventricle. Bernheim stated that the effect of such changes was partial occlusion of the right ventricular cavity by the intrusion of the septum into it, with consequent limitation of the amount of blood which the right ventricle could accept. Following this change there developed the symptoms of right heart failure. These he listed as distention of the neck veins, injection of the facial veins followed by cyanosis, edema of the lower extremities, and congestion of the liver. He said that these signs should be present in the absence of pulmonary edema.

Within recent years two reports on Bernheim's syndrome have appeared in the American literature.<sup>4,5</sup> These have helped to stimulate interest in the subject. In the first of these the sequence of the patient's symptoms was: palpitation, cough, dyspnea, orthopnea, and finally edema. Also, in one of the 3 examples presented in the second report,

the patient had the physical signs and post-mortem findings of mitral stenosis, and in both of the others there was evidence of pulmonary congestion at the physical examination when peripheral edema was first observed. Moreover, in the autopsy statistics of the latter 2 cases the liver weights were 850 grams and 1100 grams, which does not indicate passive congestion, nor are pulmonary weights included in this report. It is our opinion that inasmuch as left ventricular failure is the commonest cause of failure of the right ventricle the signs of peripheral venous congestion should precede those of pulmonary congestion if a clear cut diagnosis of Bernheim's syndrome is to be made. To this reasonable qualification should be added the elimination of lesions

Since this syndrome pertains specifically to hypertrophy of the myocardium, only those hearts weighing 750 grams or more were selected. Clinical records of these cases were used to obtain the data for our correlations.

In this series of 2000 patients there were 28 whose heart weight was in the range between 750 and 900 grams, and 5 with cardiac weights exceeding 900 grams. There were, therefore, 33 hearts which presented the picture of massive hypertrophy and weighed at least twice the normal average weight.

A breakdown of these figures showed that 29 of the enlarged hearts belonged to men, and four to women. The average age of the male patients was 54 years at the time of death, with individual ages ranging from 16 to 87 years. The ages of the females averaged 53 years and ranged from 42 to 65.

Inasmuch as the picture of right

TABLE 1. PATHOLOGICAL DIAGNOSES

Diagnosis	750-900 Grams	900 Grams or more
Hypertensive heart disease*	14	2
Rheumatic heart disease		
mitral valve disease only		1
mitral and aortic valve disease	4	2
mitral, aortic, and tricuspid valve disease	1	
Aortic stenosis, calcareous*	3	
Hypertension with mitral and aortic rheumatic valvular disease	1	
*Arteriosclerosis, coronary**	1	
Arteriosclerosis, aortic, with aneurysm*	1	
Syphilitic aortitis, with aortic regurgitation*	1	
*Ayerza's disease"	1	
*Myocarditis, chronic, of unknown etiology"	1	
Total	28	5

\* Suitable for analysis as possible Bernheim's Syndrome—22 cases.

commonly associated with right ventricular insufficiency, for example, mitral stenosis, extensive or massive pulmonary embolism, and chronic pulmonary obliterating endarteritis.

Since this so-called syndrome has lacked adequate appraisal and yet is occasionally and casually diagnosed, we have studied the clinical and post-mortem records of a series of patients with grossly hypertrophied hearts.

**Material.** The material used in this study was secured from 2000 consecutive post-mortem examinations performed between May 10, 1941 and April 27, 1946 at the Massachusetts General Hospital.

ventricular failure in patients with this complex is supposedly the result of a hypertrophic lesion of the left ventricle, the 33 grossly hypertrophied hearts had to be classified as to the etiology of their disease (Table 1.) Of the total, 22 fell into categories usually associated with enlargement of the left ventricle, as follows: hypertensive heart disease, 16; calcareous aortic stenosis, 3; aortic aneurysm due to arteriosclerosis, 1; coronary arteriosclerosis, 1; and syphilitic aortitis with aortic regurgitation, 1. These 22 could accordingly be studied as possible instances of Bernheim's syndrome; they are marked with an asterisk in Table 1.

The large hearts resulting from lesions which usually cause right heart failure

numbered 10. Rheumatic heart disease with mitral stenosis alone accounted for 1; mitral and aortic involvement, 6; mitral, aortic, and tricuspid stenosis, 1. Hypertension and glomerulonephritis were associated with rheumatic mitral and aortic stenosis in 1 case, and in 1 pulmonary endarteritis ("Ayerza's disease") was the responsible factor. Chronic myocarditis of undetermined origin was found to be the cause of enlargement in 1 heart which weighed 750 grams.

Our figures in Table 1, on the incidence of the various basic pathological lesions, are in general agreement with previous studies.<sup>3</sup> Hypertension was the most common etiological factor in these large hearts, but the very largest more often resulted from rheumatic heart disease. The 3 hearts in the rheumatic group which exceeded 900 grams in weight weighed 1350, 950, and 925 grams respectively, while the 2 exceedingly heavy hypertensive hearts weighed 920 and 900 grams each. The largest heart of the entire group (1350 grams) was one with a rheumatic deformity of the mitral valve unassociated with an aortic lesion.

peared unassociated with left in the presence of left ventricular hypertrophy.

The plan has been to analyze the 22 suitable cases from 4 points of view. First, a study was made of the initial and secondary symptoms of cardiac failure in the clinical histories. Secondly, an attempt was made to determine from the weight of the lungs and liver in a given instance whether peripheral congestion had been present without pulmonary congestion. To do this the patients with lungs of normal, or near normal, weight and with livers exceeding the normal figure were listed and the clinical record then examined to see whether the case had fitted the Bernheim criteria at the date of initial failure. Thirdly, since pronounced hypertrophy must be present to cause encroachment of the interventricular septum into the lumen of the right heart chamber, the hearts with left myocardial thickness at least twice greater than normal were studied from the point of view of clinical and pathological findings. Fourthly, as Glushien<sup>1</sup> has pointed out, this type of failure should result in en-

TABLE 2. THE EARLY SYMPTOMS OF FAILURE IN 22 HYPERTROPHIED HEARTS WITH MARKED LEFT VENTRICULAR HYPERTROPHY

First Symptoms		Second Symptoms	
Dyspnea	15	Dyspnea	7
Fatigue	5	Orthopnea	7
Faintness	2	Edema	5
Substernal oppression	2	Nocturnal dyspnea	5
Orthopnea	1	Cough	3
Edema	1	Substernal oppression	1
		Palpitation	1
		Paroxysmal fibrillation	1

In searching this group of 22 hearts with left ventricular hypertrophy for examples of the Bernheim complex several points were considered. Since the commonest cause of right heart failure is a failure of the left side, it seemed reasonable to expect the signs and symptoms of right-sided failure (venous distention, edema, hepatomegaly) to precede those of left-sided failure (dyspnea, orthopnea, paroxysmal nocturnal dyspnea) in this syndrome. Accordingly a list was made of the patients' earliest symptoms and signs of cardiac failure, of their myocardial thickness—and their pulmonary and hepatic weights, to learn the frequency with which right-sided failure ap-

pearance of the right auricle without concomitant right ventricular dilatation. This, then, was investigated in the roentgenographic examinations which had been made on these patients.

**Findings.** The examination of the clinical records of the 22 patients who were considered, because of their pathological findings, as candidates for Bernheim's syndrome, was interesting.

1. The first symptoms of heart failure to make their appearance are classified in Table 2. Only 1 patient was edematous before becoming dyspneic.

TABLE 3. LESIONS OF 22 CASES WITH MARKED LEFT VENTRICULAR HYPERTROPHY

<i>Pathology</i>	<i>Total Heart Weight (Grams)</i> 250-350*	<i>Left Ventricle (mm.)</i> 10-12*	<i>Thickness of Wall Right Ventricle (mm.)</i> 3-4*	<i>Weight of Lungs (Grams)</i> 900-1230**	<i>Weight of Liver (Grams)</i> 1440-1680**
Normal	No.				
Hypertension	1 780	23	8	1600	2200
	2 900	23	10	1300	2750
	3 800	17	9	2600	1680
	4 920	25	10	1675	2300
	5 780	18	5	740	1320
	6 790	15	5.5	1000	1000
	7 785	23	6	910	1320
	8 870	26	8	940	2550
	9 850	24	8.5	2150	2100
	10 810	24	6	980	1530
	11 800	20	6	1800	2400
	12 800	20	6	1200	2300
	13 840	20	10	1750	1800
	14 840	16	7	2750	1900
	15 890	15	6	1850	1750
	16 750	20	4	1320	1800
Av.	825	21.1	7.1	1535	1918
Aortic Sten. calcareous	17 825	15	9	1500	1500
	18 800	22	5.5	1170	1400
	19 850	22	7	1100	1470
Av	825	19.6	7.1	1285	1123
Arteriosclerosis coronary	20 775	15	8	1250	2300
Syphilitic	21 750	25	6	2000	2000
Arteriosclerosis aortic	22 750	16	5	1340	2750
Average	816 Gm.	20.6 mm.	7.1 mm.	1406 Gm.	1914 Gm.
* Ref. 8.					
** Ref. 9.					

All who had edema as a second symptom of incompetence had had preceding dyspnea, and in most instances a second symptom of left ventricular failure appeared simultaneously with edema, so that they could hardly be classed as primary right heart failure.

The one patient with edema listed as the initial symptom is recorded as No. 6 in Table 3. From both clinical and pathological standpoints there were substantial reasons for objecting to a diagnosis of the syndrome in his case. The patient was unable to give a history, and what information was known was supplied by his physician, who had seen him but once, briefly, at the time he was sent to the hospital. He was said to have had ankle swelling for 2 weeks only. On admission he had massive pitting edema as high as the sacrum, enlargement of the liver, and cervical venous distention, but in addition moist rales filled the lower

halves of both lung fields and auricular fibrillation was present. At post-mortem examination neither the lungs nor liver were sufficiently congested to be of more than normal weight. Besides hypertensive renal disease, age (87 years), arrhythmia, and severe emaciation contributed to this man's failure. He also had thrombosis of the pelvic veins and infarction of the right lower lobe of the lung. In view of all these discrepancies, a diagnosis of Bernheim's syndrome would be poorly founded.

2. In Table 3 pathological values of the 22 patients are given for purposes of evaluation. In the list there are 6 instances (Nos. 2, 8, 12, 16, 20, 22) of the association of a heavy liver with lungs of normal or nearly normal weight. The clinical data for these particular patients are listed in Table 4, since from the pathological findings

TABLE 4. EARLY EVIDENCE OF CARDIAC FAILURE IN 6 CASES SELECTED AS POSSIBLE BERNHEIM'S SYNDROME

Case No.	Symptoms of Failure		Signs of Failure			Laboratory Data		Remarks
	First	Second	Cervical venous disten.	Lungs Moisture	Extremities Edema	Ecg.	X-Ray	
	Dyspnea	Orthopnea and ankle edema	0	Musical rales bilaterally	Enlargement Edge 2 fingers below costal margin	Present	Diph. T <sub>1</sub> 2, flat T <sub>2</sub> Sag. S-T <sub>1</sub> 3; L.A.D.	Fluid in left costophrenic angle. Ill. increased in region of left ventricle
8	Dyspnea and fatigability	Orthopnea and parox. noct. dysp.	0	0	0	0	L.A.D.; low T <sub>1</sub> , later both inv.	Followed 1/20/40 to 11/6/41. Lungs never clear on subsequent admissions. Post-mortem examination showed marked pulmonary edema.
12	Dyspnea and faintness	Cyanosis	Slight disten.	0	0	Slight trace	S.A. Tachy. P-R 0.25; inv. T <sub>1</sub> diph. T <sub>2</sub> low T <sub>3</sub>	Followed 1/9/40 to 3/28/41. Edema with congestive failure at final admission.
16	None	None	0	0	0	0	Left vent. strain	Seen 6/19/42. Died 6/23/42. P <sub>2</sub> +. Hemipericardium and tamponade. Dissecting aortic aneurysm.
20	Fatigability and dyspnea	Parox. noct. dyspnea	0	0	0	0	Q <sub>0</sub> -T <sub>3</sub> pattern	Followed 2/8/45 to 3/25/45.
22	Fatigability and dyspnea	Orthopnea	0	0	0	0	Left vent. strain T <sub>1</sub> late inversion	Followed 5/1/31 to 10/10/41. Edema and rales terminally.
O = Normal.								

Followed 12/3/41 to 7/10/45. Never showed signs of right heart failure.



one might expect them to have had right heart failure in the absence of left. As may be seen, the 5 with symptoms of failure had dyspnea as the initial complaint of insufficiency, and in 3 the second manifestations of incompetence were those of left ventricular weakness, namely, orthopnea and paroxysmal nocturnal dyspnea. One patient, No. 2, had edema as his second cardiac symptom, and although it was associated with orthopnea he might be expected to show some of the features of Bernheim's syndrome. However, this was not the case, since he had had no distention of the cervical veins and at every physical examination during the course of his illness pulmonary rales had been heard. At autopsy the pathologist found marked pulmonary edema present. Patient No. 12 did have cyanosis, some congestion of the cervical veins, and a slight trace of edema of the lower ex-

ventricular myocardium measured 20 mm. in thickness as compared with 4 mm. on the right, an excellent example of "eccentric hypertrophy."

3. Patients showing the greatest degree of left ventricular hypertrophy should be the ones to show the features of this symptom complex. For this reason all those with a left ventricular wall thickness of 24 mm. or more, twice the normal value, were selected and listed in Table 5. These patients correspond to Nos. 4, 8, 9, 10, 11, and 21 in Table 3. Only one (No. 9) had any evidence of right-sided failure, and this was peripheral edema which occurred subsequent to the onset of fatigue and dyspnea. Even though there was passive congestion of the liver and that organ exceeded its normal weight, the preponderant nature of the failure in the pulmonary circulation can be deduced from the fact that the weight of the lungs out-

TABLE 5. INCREASED LUNG AND LIVER WEIGHTS IN RELATION TO EARLY SYMPTOMS

Case	Lung Weight Exceeding Normal	Liver Weight Exceeding Normal	First Cardiac Symptom	Second Cardiac Symptom
4	x	x	fatigue	palpitation
8		x	dyspnea	dyspnea
9	x	x	fatigue	paroxysmal nocturnal dyspnea
10		x	dyspnea	orthopnea
11	x	x	pain	edema
21	x	x	dyspnea	dyspnea
			nocturnal substernal oppression	orthopnea
				paroxysmal nocturnal dyspnea

tremities. Though there were no pulmonary rales, his second heart sound in the pulmonic area was accentuated, suggesting excessive pressure within the lesser circuit. At post-mortem examination he was found to have cardiac tamponade due to a dissecting aneurysm which extended to the pericardium, the neck vessels above, and the iliac vessels distally. His acute illness lasted only four days. One patient of the six (No. 16) had never had symptoms of failure, although his left

weighed that of the liver at post-mortem examination.

4. Seventeen of the 22 patients with primary left ventricular hypertrophy had one or more Roentgen-ray examinations. Seven had general cardiac enlargement, seven showed enlargement in the region of the left ventricle, 4 had dilatation or tortuosity of the aorta, and 1 had cardiac dimensions which were reported as normal. None of the 17 had any lesion interpreted as right auricular dilatation.

**Discussion.** In this series of cases analyzed from several points of view no clear cut case of Bernheim's syndrome could be found, even in a group of hearts selected particularly for the presence of left ventricular hypertrophy of an advanced degree. The same was true of those with post-mortem findings suggesting hepatic congestion without pulmonary edema. Roentgen studies and symptom analysis did not yield any evidence favoring a diagnosis of Bernheim's syndrome. On theoretical grounds also Bernheim's syndrome would seem unlikely. The thin-walled right ventricular cavity should be able to dilate sufficiently as a crescent-shaped chamber overlying the left ventricle so that there need be no obstruction to blood flow through it.

Furthermore, in some of the cases already recorded as showing Bernheim's syndrome, actual pulmonary embolism or other cause of increasing pulmonary blood pressure has been casually and without warrant disregarded as an important factor favoring right heart failure in the absence of left heart failure.

**Summary and Conclusions.** The study of a group of 33 hearts weighing more than 750 grams showed that hypertensive heart disease was the etiologic agent in 16, while rheumatic heart disease with mitral stenosis alone, or with aortic valve involvement, was responsible for 8 and for the largest of those examined. In the remainder the causes of enlargement were: calcareous aortic stenosis in 3, and, in 1 each, hypertension with rheumatic heart disease, "coronary arteriosclerosis," "arteriosclerosis of the aorta with aneurysm," syphilitic aortitis with aortic regurgitation, "Ayerza's disease," and "chronic myocarditis."

In the hearts of the group with left ventricular hypertrophy no instance could be found of isolated early signs or symptoms of right-sided failure. We concluded from this analysis, as well as from prior experience, that we have yet to encounter any unquestionable case of so-called Bernheim's syndrome. It would appear sensible to drop this designation unless proof can be adduced to support it.

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# AN EVALUATION OF ESOPHAGEAL ELECTROCARDIOGRAMS IN THE DIAGNOSIS OF HEALED POSTERIOR MYOCARDIAL INFARCTION\*

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THE correct clinical interpretation of a prominent downward deflection at the beginning of the initial ventricular deflection in standard Lead III remains most difficult. When typical electrocardiographic QRS patterns exist, wherein the left leg is initially negative to both the right arm and the left arm with a resulting  $Q_2$  and  $Q_3$ , the picture may be diagnostic of a previous infarction located in the posterior or diaphragmatic wall of the heart. When only a deep  $Q_3$  is present, interpretation of it in respect to previous infarction tends to become a question of statistical probability. Many investigations have been carried out to differentiate the "normal" and "pathologic"  $Q_3$ , and many aspects of the problem have been clarified. Perhaps, as similarly located electromotive forces may be operative in causing both types of Q wave, and as, in some cases, the effects may be additive, it might be better to classify a  $Q_3$  as not significant, or significant of previous infarction. It is important that apparently rather minimal scarring of the posterior diaphragmatic wall of the left ventricle may cause a significant  $Q_3$  but that a  $Q_3$  does not reflect "coronary disease" in the absence of previous myocardial infarction.

Any electrocardiographic method that would clarify the problem of the lengthened Q when such is the only

electrocardiographic relic of infarction would be very worth while. The use of extremity unipolar potentials,<sup>5,11</sup> according to the method of Wilson, or an augmented extremity potential obtained by disconnecting the limb explored from the central terminal<sup>1,2</sup> has made the conception of the problem easier. The so-called left leg augmented unipolar extremity lead, namely the recorded changes of the potential of the left leg relative to the mean potential of the two upper extremities, has been of considerable value.<sup>7,8</sup> Absence of a Q wave in this lead is strong evidence against a previous posterior myocardial infarction. However, the interpretation of Q in this lead frequently needs to be made with the same caution and statistical approach, particularly if one's patients include many with hypertension, as are used in interpretation of the Q wave in standard Lead III.<sup>6</sup>

Experience at the Mayo Clinic with esophageal electrocardiography in attempting to elucidate the  $Q_3$  problem has been scattered over the past 10 years, beginning after the study of Hamilton and Nyboer.<sup>3</sup> The use of small but heavy electrodes with thin flexible lead wires has made the problem easier for the patient, who may either swallow the electrode like a capsule or allow it to pass down the throat when it is introduced through the nose. For comparison of esophag-

\* Read at the sectional meeting of the American Federation for Clinical Research, Chicago, Ill., Oct. 10-12, 1947.






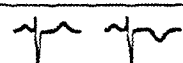
eal electrocardiograms made at different levels it has been helpful to use multiple electrodes at fixed distances along the small-caliber flexible plastic tube which carries the insulated lead wires. In the past year or more a direct writing electrocardiographic machine has greatly facilitated the exploration of the electric field of the esophagus and stomach. In the records of recent years the indifferent electrode has been the central terminal of Wilson, and an upward deflection on the graphic record has represented relative positivity of the esophageal electrode.

Early experience indicated that the value of esophageal leads in the diagnosis of healed posterior myocardial infarction was slight when compared to the exceptional usefulness of precordial leads in old infarction of the septum, apex and lateral walls of the left ventricle. It has not been possible to obtain correlation studies of the esophageal electrocardiogram and the pathologic anatomy of the heart in our

group of subjects as no patient has died within a year of the time the esophageal electrocardiograms were taken. It was apparent that great caution had to be exercised regarding the interpretation of deep Q waves, with or without a following R wave, and of inverted T waves of the esophageal electrocardiogram even when the electrode had seemed to be at the ventricular level as judged by the absence of an intrinsic type of wave in the P wave. However, from the study of the early tracings made at the clinic in 1938 and 1939 by me, it was evident that in some cases the electrode probably had not been passed deeply enough into the esophagus or upper part of the stomach to explore completely the type of ventricular complexes at low esophageal and gastric levels. Due to the great variations in the length of the neck and thorax, actual distances from the teeth or nares are not definitely significant except for repeated studies of the same person.

A group of 50 cases in which esophag-

ESOPHAGEAL ELECTROCARDIOGRAMS AT THE VENTRICULAR LEVEL

Type	Electrocardiographic pattern	Number of cases	Angina without clinical infarction	Previous infarction*	Diagnostic Q <sub>2</sub> Q <sub>3</sub> T <sub>2</sub> T <sub>3</sub> pattern
A		6	2	3	2
B		12	1	4	2
C		19	6	5	1
D		6	1	2	2
E		4	2	2	1
F		3	1	2	1
Totals		50	13	18	9

\* Typical history or previous registration with clinical diagnosis and ECG changes

Fig. 1. The various patterns of esophageal electrocardiograms obtained in persons who had had posterior myocardial infarctions or whose electrocardiograms might cause one to suspect the presence of such a condition. The difficulties encountered when tracings are made with the electrode near the atrioventricular junction are discussed in the text.

eal electrocardiograms were made has been chosen for the purpose of determining the probability of obtaining diagnostic esophageal electrocardiograms in cases in which the history and electrocardiograms at the time of an acute episode indicated previous acute myocardial infarction and in cases in which only angina pectoris or a deep  $Q_3$  in the electrocardiogram was present. In addition, some technical difficulties which the beginner in esophageal electrocardiography might encounter are mentioned.

The electrocardiographic and diagnostic data are consolidated in Figure 1. Of the 50 patients, 18 were believed to have had an acute myocardial infarction, and in half of these 18 a late diagnostic  $Q_2Q_3T_2T_3$  pattern had re-

sulted which was present at the time of the esophageal electrocardiographic study. Thirteen patients had angina pectoris without any clinical evidence on which to suspect infarction, and the other 19 were without clinical evidence of coronary disease. Of these 19 patients 16 showed deep Q waves in standard Lead III and the remaining 3 had deeply inverted T waves in Leads II and III with the "electrocardiographically vertical" variant of the left ventricular strain pattern.

It is apparent that the esophageal tracing may present a variety of appearances in the presence of a posterior myocardial scar, in both the presence and the absence of other electrocardiographic evidence of the previous infarction. The electrocardio-

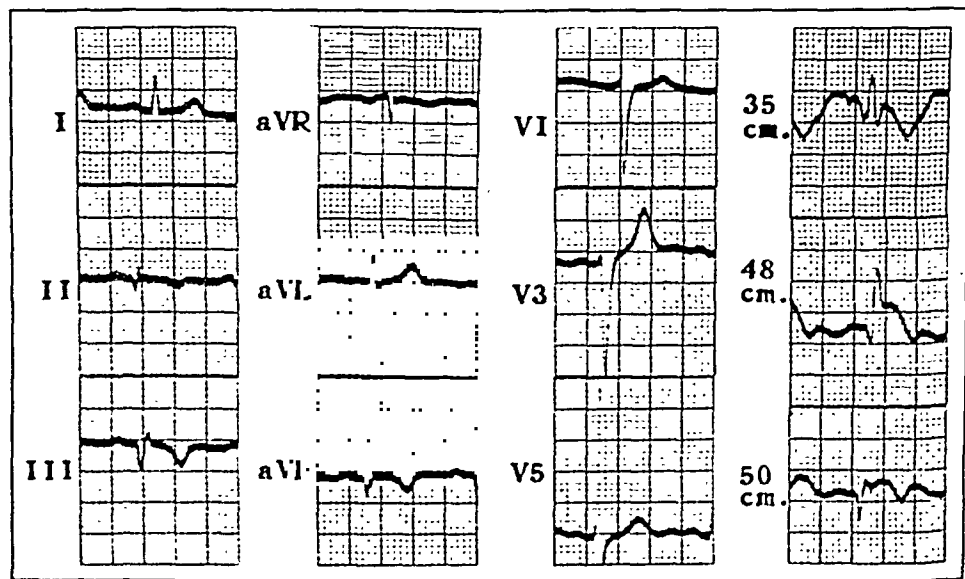


Fig. 2. Esophageal electrocardiograms illustrating a diagnostic pattern of old posterior myocardial infarction. The standard leads and aVF present typical evidence for such a diagnosis in themselves. The similarity of the esophageal tracing made with the electrode at a distance of 50 cm. from the teeth to tracings made with the electrode on the precordium of patients who have had an anterior infarction is evident. The tracings were obtained on a man of 52 years who had no symptoms but who had had an attack of severe chest pain two years previously with typical electrocardiographic evidence of acute posterior myocardial infarction at that time. In this and subsequent figures, the standard electrocardiographic leads in the column on the left are designated by Roman numerals. The "augmented limb potentials" of the right arm, left arm and left leg from above downward on the second column are indicated by the symbols aVR, aVL, and aVF. In the third column are chest leads from the 1, 3 and 5 precordial positions, using as the indifferent electrode the central terminal of Wilson. In the last column are esophageal electrocardiograms obtained at the distances from the teeth indicated.

graphic patterns most to be relied upon as indicating an old infarction are those indicated under E and that shown under D in Figure 1 and having the inverted T wave (Fig. 2 and Fig. 3). Pattern A is the characteristic QRS and T observed at atrial levels but if it persists at lower levels it is indicative of previous infarction. Patterns B, C, and F may occur in a group of persons without coronary sclerosis. The negative T waves in these patterns (Fig. 4), when not reflecting coronary disease, are largely related to the group of patients in which there are many hypertensive individuals, a relationship that was early recognized by Nyboer.<sup>9</sup>

**Comment.** The close similarity between the normal ventricular complexes at atrial levels and ventricular com-

plexes characteristic of posterior myocardial infarction at infra-atrial levels in esophageal electrocardiograms may make interpretations of single esophageal tracings difficult. The length of the transitional zone in different types of cases requires further study, as Q and QR deflections characteristic of atrial levels may sometimes persist below the level where the P waves no longer show definite intrinsic deflections (Fig. 5). The problem is more difficult when one is inquiring into the probabilities of previous infarction in patients having associated valvular or hypertensive disease than when one has to decide only between complete normality and deviations therefrom. It might be thought that esophageal electrocardiograms would be more

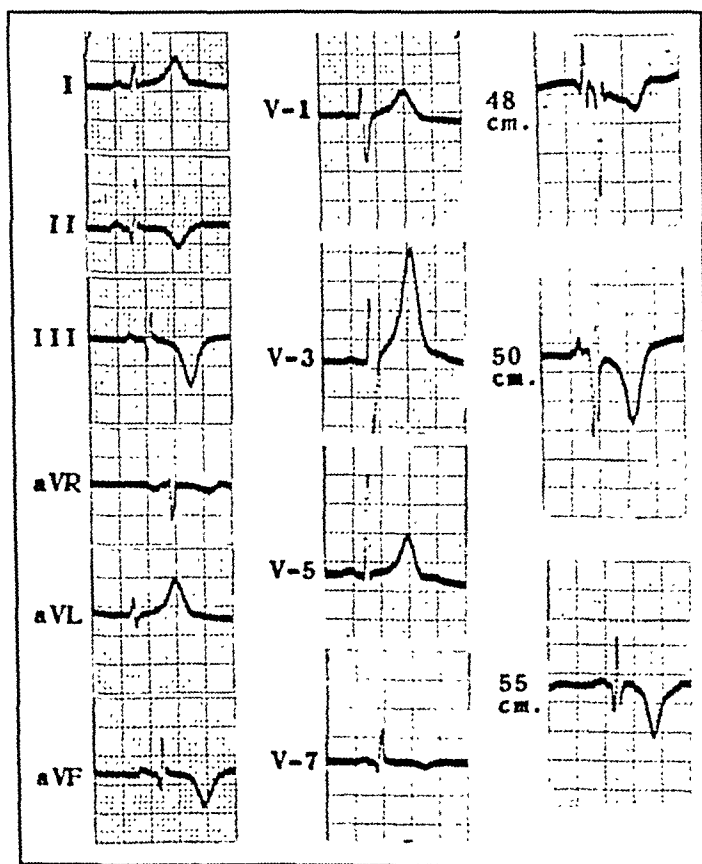


Fig. 3. The typical pattern of old posterior infarction in the standard leads and in aVF. The reciprocal high voltage T waves of the mid-precordial leads and the esophageal lead are to be particularly noted. A deep Q wave with a W-shaped QRS is present in the latter lead. The patient was 39 years of age and had had severe crushing thoracic pain lasting 8 hours, 4 weeks previous to his examination.

likely to give a characteristic infarction picture in the case of hearts that are in a more vertical position, the left ventricular wall being in closer proximity to the esophagus, than in the case of hearts that lie in a more horizontal position; but preliminary observations have given no definite support to such a supposition. This has been true in regard to the anatomic position of the heart as judged by roentgenograms and by the "electrocardiographic position" as determined

tained near the diaphragmatic level as has been pointed out by Helm, Helm and Wolferth.<sup>4</sup> They also found that cavity potentials which they term the "endocardial" pattern may influence the esophageal electrocardiogram at infra-atrial levels. Their opinion that little advantage would be obtained by recording the diaphragmatic pattern in the esophagus in addition to that of the surface of the leg receives some, but not complete, support by my investigations. In particular, in some

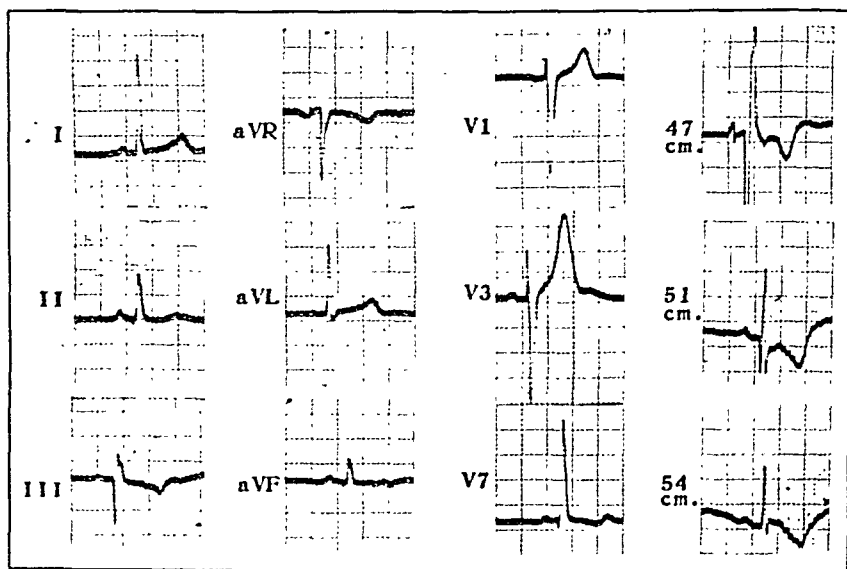


Fig. 4. Electrocardiograms in which a Q<sub>i</sub> is a predominant feature in the standard leads. No Q wave is present in aVF or in the esophageal lead at 54 cm. The Q<sub>i</sub> is explained by high positive potential of the left arm relative to the left leg. The negative T wave in the esophageal lead at the lower level may be explained by the left ventricular hypertrophy. However, a posterior myocardial scar could have been a causative factor in production of the negative T wave of this esophageal lead as well as the high positive T wave in V<sub>1</sub>, as in some patients with known previous posterior infarctions reciprocal high voltage T waves in V<sub>1</sub> and esophageal leads at the ventricular level have been a characteristic finding. The patient was 61 years of age, with angina pectoris of 7 years duration and a blood pressure averaging 185 systolic and 110 diastolic.

by the precordial leads and extremity potentials. In all but a few cases, the configuration of the esophageal electrocardiogram at the ventricular level has tended to approximate the configuration of the left leg extremity potential. The fact that there has been this resemblance is strong evidence that the esophageal tracings were ob-

patients with right bundle-branch block associated with an old posterior infarction the esophageal leads have given useful confirmatory evidence (Fig. 6) similar to the evidence obtained from localized precordial leads in the situation in which right bundle-branch block is associated with an old anterior infarction. While it has been

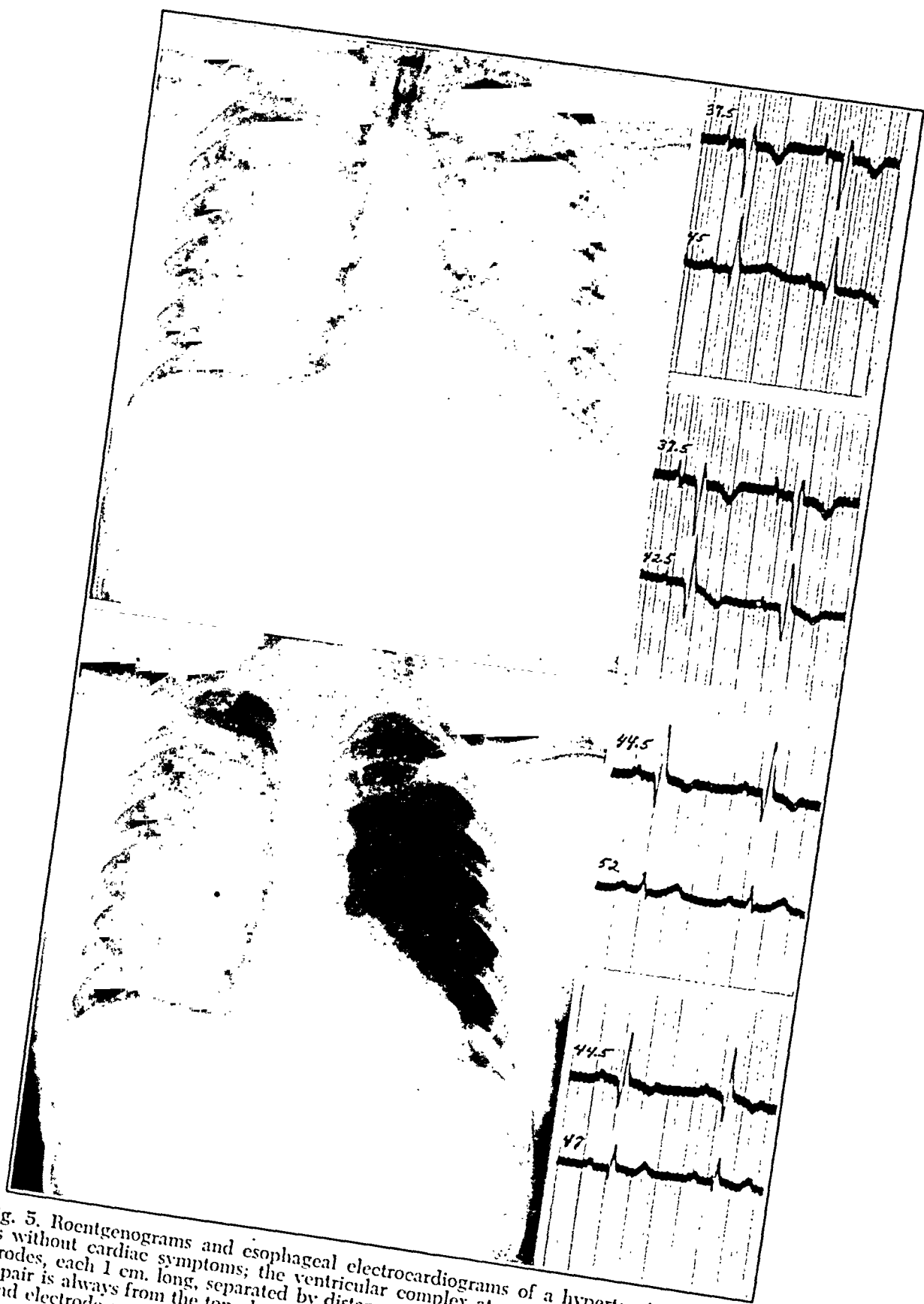


Fig. 5. Roentgenograms and esophageal electrocardiograms of a hypertensive patient of 38 years without cardiac symptoms; the ventricular complex at various levels is illustrated. Four electrodes, each 1 cm. long, separated by distances of 1.5 cm., may be seen. The top tracing of each pair is always from the top electrode. The tracings in the upper group were obtained when the end electrode was 45 cm. from the anterior nares, the lower group when the end electrode had been advanced a further 7 cm. If the electrodes are numbered from 1 to 4 from above downward, the pairs of tracings, from above downward, were taken from the electrodes 1 and 4, 1 and 3, 1 and 4, and 1 and 2 respectively. In the upper group the narrowness of the zone, from 42.5 to 45 cm., through which a marked change occurs in the ventricular complex, is to be noted. In the lower group the bottom pair of electrocardiograms made with electrodes at 44.5 and 47 cm., respectively, show a similar change. The tracings also illustrate the fact that one cannot use distance from the nares as the basis for reproducing exactly the same tracing, as the differences in the tracings in the upper and lower groups labeled 45 and 44.5 cm., which occurred as a result of the slight measured variation of only 0.5 cm., are evident.



proved by Myers and Oren<sup>8</sup> that a deep Q wave in relation to the R wave in the esophageal electrocardiogram may reflect the presence of a posterior myocardial scar, such proof would be expected to be more readily available than in a case in which the Q wave might not be reflecting such a scar, the former patient being the more likely to die. In their analysis of the significance of a Q<sub>3</sub> pattern Myers and Oren used esophageal leads to establish the diagnosis of previous infarction in 11 of their 25 cases and to exclude such an infarction in 22 of the 25 cases in their control group. Such universal definiteness in the diagnosis or in the exclusion of previous posterior myo-

The separation of the recorded esophageal electrocardiograms into the patterns described is purely arbitrary, there being no clear-cut division between the various types. The variability in these esophageal electrocardiograms probably indicates that some were made with the esophageal electrode near the zone of transition when the ventricular type of esophageal electrocardiogram was obtained. When the electrode is in the stomach less variability is encountered. With the electrode in the stomach, it was observed in one patient with suspected old posterior infarction that the Q wave increased as the patient leaned forward from the sitting position. In other

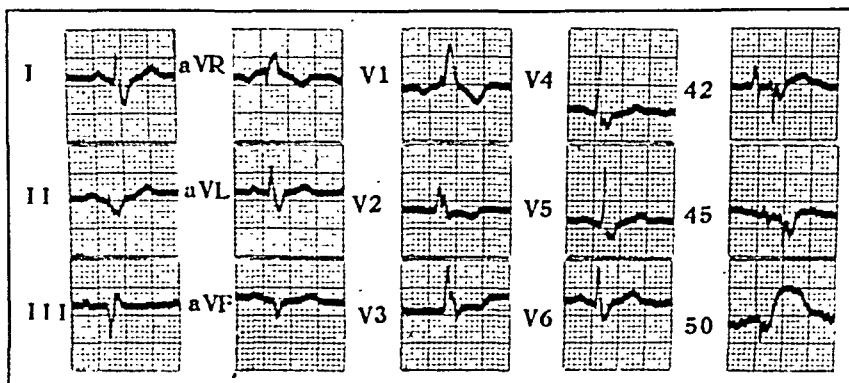


Fig. 6. Electrocardiograms, made on a patient 63 years of age, interpreted as indicating right bundle-branch block and previous infarction of the posterior ventricular wall. A characteristic history of angina pectoris of two years' duration was obtained. Nocturnal angina had been present. None of the attacks of pain had exceeded five minutes in duration.

cardial infarction by esophageal electrocardiograms has not been possible in my experience.

The problem of interpretation of the esophageal electrocardiogram may be likened to the problem of interpretation of precordial leads in the 1, 2, 3 position of the exploring electrode. Absence of R waves and negativity of the T wave in these precordial leads often have to be interpreted in relation to the tracings made with the electrode also in the 4, 5 and 6 positions.

patients, it was impossible to bring out a completely diagnostic picture in the esophageal or gastric electrocardiograms with the patient in many decubitus positions. The various positions of the double electrode in one patient are shown in Figure 7. Deep inspiration and expiration cause marked differences in relative positions of the electrode and heart but any particular phase of respiration did not have diagnostic importance.

The adoption of esophageal electrocardiography for diagnostic pur-

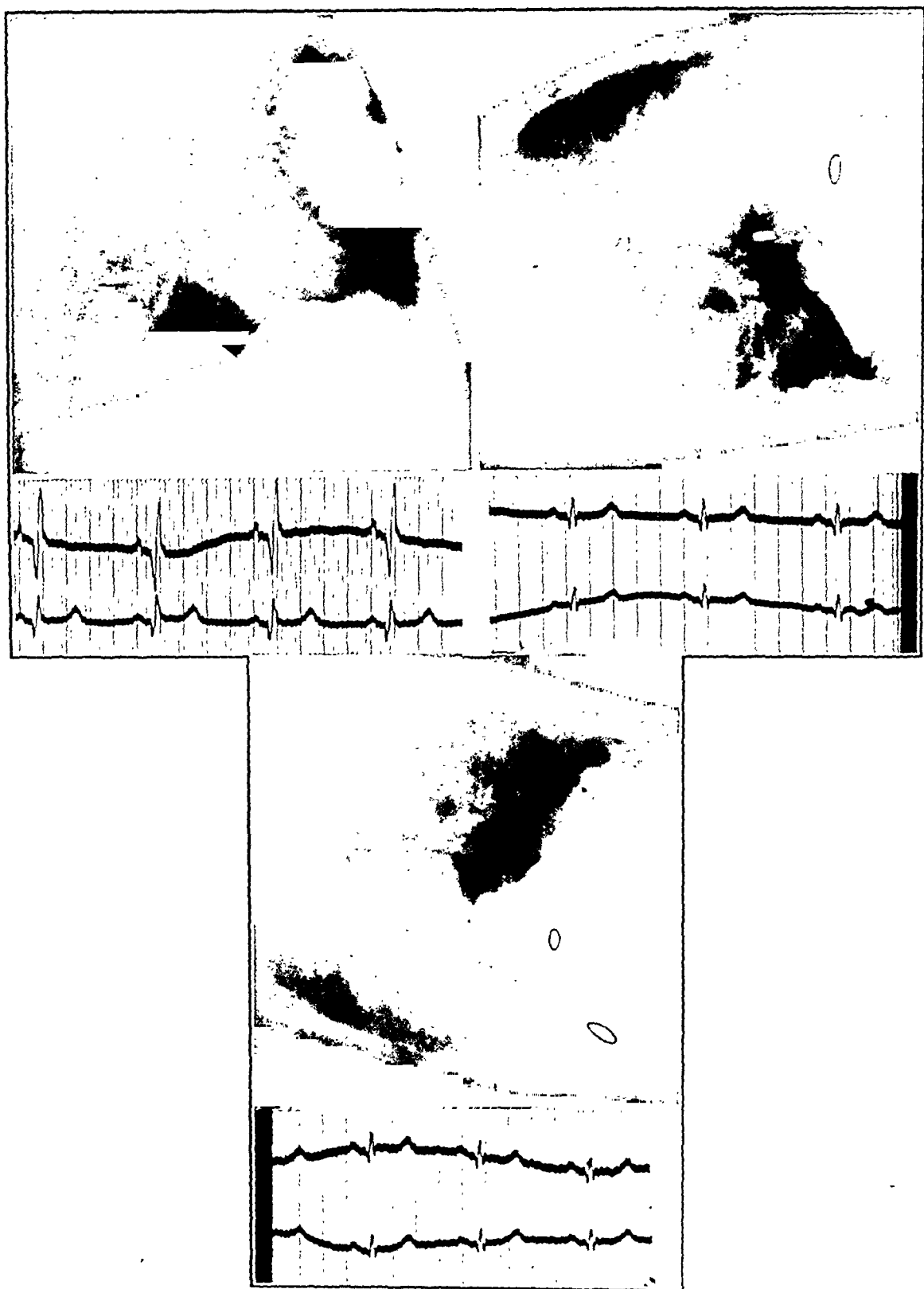


Fig. 7. Roentgenograms and electrocardiograms made on a patient 61 years of age who had had myocardial infarction of the posterior type 18 months previously. The first tracings and roentgenogram were made with the patient in the sitting position and then the electrode was advanced a further 5 cm. and tracings and roentgenograms were made with the patient in the supine and prone positions. There was a residual Q pattern in Leads II, III, and aVF, which could be interpreted as assumptive evidence of the old infarction, but the esophageal and intra-gastric electrocardiograms are more equivocal. The electrodes are 5 cm. apart and, when intra-gastric, change in position when the patient moves from the supine to the prone position causes no significant change in the electrocardiogram. The tracings were made at half normal sensitivity.

poses has been slow, which is probably related to difficulties in readily obtaining tracings of this type and to difficulties in their interpretation. The more definite criteria<sup>10</sup> given for the normal and infarction patterns of esophageal electrocardiograms may lead to more widespread use of this method. At the present time it is difficult to know the exact meaning of small Q or negative T waves in esophageal electrocardiograms of patients who have borderline normal electrocardiograms or cardiac enlargement. The possible dangers of inducing cardiac damage if the patient gags and strains at the time of the introduction of the electrode are believed minimal, but, in the few patients who have had significant difficulty, the attempt to obtain these special electrocardiographic leads has been abandoned.

**Conclusions.** Electrocardiograms made with the electrode in the lower part of the esophagus and stomach are sometimes of great value in confirming a diagnosis of healed posterior

myocardial infarction. but sometimes they are normal or are not definitely diagnostic even when the heart is known to contain a scar in the posterior myocardial wall. Esophageal electrocardiograms which might be regarded as diagnostic of old posterior myocardial infarction, particularly those with QS deflections followed by a deeply inverted T wave, have usually been associated with a suggestive or diagnostic Q<sub>2</sub>Q<sub>3</sub> pattern in the standard leads in this study.

While the transitional zone through which the types of ventricular complex characteristic of atrial levels and of ventricular levels are obtained is usually narrow, in some instances the former type of complex may tend to persist when the atrial complex contains no intrinsic type of deflection.

When esophageal leads are used to elucidate the clinical significance of a deep Q<sub>2</sub> in cases in which such a Q<sub>2</sub> is the only finding leading to the suspicion of previous myocardial infarction, the findings are frequently of equivocal nature.

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# FAMILIAL INTERAURICULAR SEPTAL DEFECT WITH MITRAL STENOSIS (LUTEMBACHER'S SYNDROME)\*

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WE have under observation two sisters, aged 21 and 25 years, presenting evidence of heart disease of remarkably similar nature. Both have typical physical and Roentgen-ray findings of interauricular septal defects and complicating mitral stenosis (Lutembacher's syndrome)—a familial occurrence that we have not found previously reported.

**REVIEW OF THE LITERATURE.** Sixty-three reports describing the occurrence of congenital heart disease in 2 or more members of a family have been encountered in a review of the literature of this subject. Of these, 37 appeared in the review by Medvei and Roesler<sup>14</sup> (1932) which included 3 examples of their own, involving in each case 2 members of a family. In addition Snelling<sup>20</sup> (1937), in presenting his case reports of 2 sisters with the clinical diagnosis of patent ductus arteriosus, included a translation of Tedesco's<sup>25</sup> review (1933), which mentioned 5 other examples of familial congenital heart disease not discussed by Medvei and Roesler. Case reports which have appeared since then describe familial congenital lesions other than interauricular septal defects, for example, patent ductus arteriosus, coarctation of the aorta, interventricular septal defect, pulmonic stenosis<sup>5,6,8-11, 13, 18, 19, 22, 23, 28-33</sup>.

In this review we were unable to find any mention of familial Lutembacher's syndrome. This is not surprising since reports of this syndrome are quite infrequent.

More surprising, however, was the absence of any report of a familial occurrence of uncomplicated interauricular septal defects. This seems striking since auricular septal defects, usually simple patency of the foramen ovale, are the most common of congenital cardiac defects.

In 2 reports, accompanied by pathologic description, patency of the foramen ovale occurred in 2 members of a family in conjunction with other more serious defects. The earliest reported example of familial congenital heart disease is that of Cooper and Englenot (1818). As quoted by Medvei and Roesler<sup>14</sup>, they described a family of 12 children. Two children who died were found to have multiple congenital cardiac anomalies, in which patency of the foramen ovale was included. The second example in Medvei and Roesler's report<sup>14</sup> described 2 male infants, 5 and 3 weeks old respectively, who had patency of the ductus arteriosus and of the foramen ovale. In another report<sup>11</sup> there occurred in 1 of 2 infant sisters a defect of the interauricular septum which was overshadowed by more harmful cardiac lesions.

\*This study has been made possible by a grant in aid from the Life Insurance Medical Research Fund.

No autopsy was performed on the other sister but her cardiac lesions were thought to be similar.

We therefore believe that our cases represent the first report of familial interauricular septal defect uncomplicated by other congenital abnormality (accepting that the mitral stenosis in our cases is acquired), as well as the first report of familial Lutembacher's syndrome.

**CLINICAL REPORT OF CASES.** *Family History:* The family of which these 2 girls are a part is of German extraction, living originally in Virginia, and moving to this community when the oldest girl (Case 2 in this report) was 1 year old. There is no family history of disease on the maternal side, all relatives dying in old age. Two brothers and 1 sister of the father died of tuberculosis. At the present time the father is separated from the family, his whereabouts unknown. He has been a chronic alcoholic, engaging in periodic drinking bouts over the last 20 years. His hospital chart mentions no abnormal physical findings on 3 careful examinations on 2 different services, when he was seen here 5 years ago with the complaint of difficulty in swallowing.

Other members of the family are normal physically. The mother and 2 sisters, ages 16 and 23, have been examined and no abnormalities were found. A brother, 18, is now serving in the Army. No siblings have died.

During each of the 5 pregnancies the mother had symptoms of toxemia with nausea, vomiting, severe headaches, and marked ankle swelling. These grew more severe with successive pregnancies. Convulsions never appeared. There was no history of infectious diseases, such as rubella, at any time during her pregnancies.

*Case 1.* R. D. S., 21 years old, was the third child. Her mother states that her birth was regarded as an easy "instrument" delivery, and that the early development of the patient was normal. Walking began at the age of 16 months. She was not a "blue baby." Difficulty appeared while in the first grade as she was repeatedly excused from strenuous games because of shortness of breath and easy fatigue. The mother first noted the above symptoms 3 years later stating that occasionally the patient seemed in addition "blue around the lips and nose" on performing simple household tasks. She was examined by the school physician and

disqualified for further gymnastics because of a "bad heart."

Soon afterwards she developed her first severe illness, a "strep throat" with pain in her left shoulder. Neither the patient nor her mother recall pain in other joints. She became very weak, and bed rest for 1 year was prescribed by the family doctor, because of "rheumatic fever." When 17 she was again forced to rest in bed for a shorter period because of recurrence of the same symptoms.

For the last 4 years her activity has been limited by easy dyspnea, fatigue, and usually constant, but mild, ankle edema, which because of increasing severity led to her referral to this clinic. For the last 2 or 3 months she has had a loose, non-productive cough. On 3 occasions digitalis has been without effect on her dyspnea or ankle edema.

On physical examination the first impression was one of a definite immaturity in development. There was no cyanosis, clubbing of the fingers and toes, or neck vein distention. Blood pressure in all 4 extremities was the same, 100/70. There was a definite bulge of the rib framework of the left chest with marked increase in cardiac pulsations over the apex. There were systolic and diastolic thrills felt in the 6th and 7th interspaces in the left anterior axillary line. Enlargement of the heart to the left was confirmed by percussion. Auscultation at the apex revealed a harsh systolic murmur and a low pitched rumbling diastolic murmur with marked presystolic accentuation, ending in a loud snapping first heart sound. These murmurs were best heard in the 7th interspace in the left anterior axillary line, but were present over a large area of the lower chest as high as the 4th left interspace. A moderate systolic murmur was present in the 1st and 2nd interspaces to the left of the sternum. This murmur was not transmitted. There was an accentuated and split pulmonic second sound.

There was no demonstrable enlargement of the liver and no ascites was present.

The blood picture was slightly unusual in that 10% eosinophilia was present, for which there is at present no explanation. Urinalysis revealed 1 plus albuminuria.

The electrocardiogram showed distinctly abnormal P waves.  $P_{1,2}$  were notched and 0.13 seconds in duration.  $P_{3,4}$  were inverted. The PR interval was 0.18 seconds. There was normal axis deviation and  $ST_4$  was elevated 1.5 millimeters with  $T_4$  diphasic (Fig. 1, A).

Phonocardiography confirmed the auscul-

tatory findings. The tracing taken over the pulmonic area showed a systolic murmur with splitting of the second sound (Fig. 1, C). Over the mitral area the tracing showed the loud first sound with a systolic murmur of low amplitude and a long diastolic murmur of the type seen in mitral stenosis (Fig. 1, D).

Fluoroscopic and radiographic examination of the chest was reported as follows: "The transverse diameter of the heart is only moderately increased. The configuration is, however, markedly abnormal. The aortic knob is not demonstrable and leaves no imprint

on the barium filled esophagus in any view. In the frontal view there is marked convexity in the region of the pulmonary conus. The right and left pulmonary arteries are greatly enlarged but there is little pulmonary congestion. The barium filled esophagus is not displaced. In the right oblique view the barium filled esophagus is deviated slightly posteriorly in the region of the left auricle. A small bulge is seen behind the esophagus low on the posterior contour. This is thought to represent right auricular enlargement. Again the marked enlargement in the conus region is seen. In the left oblique view there

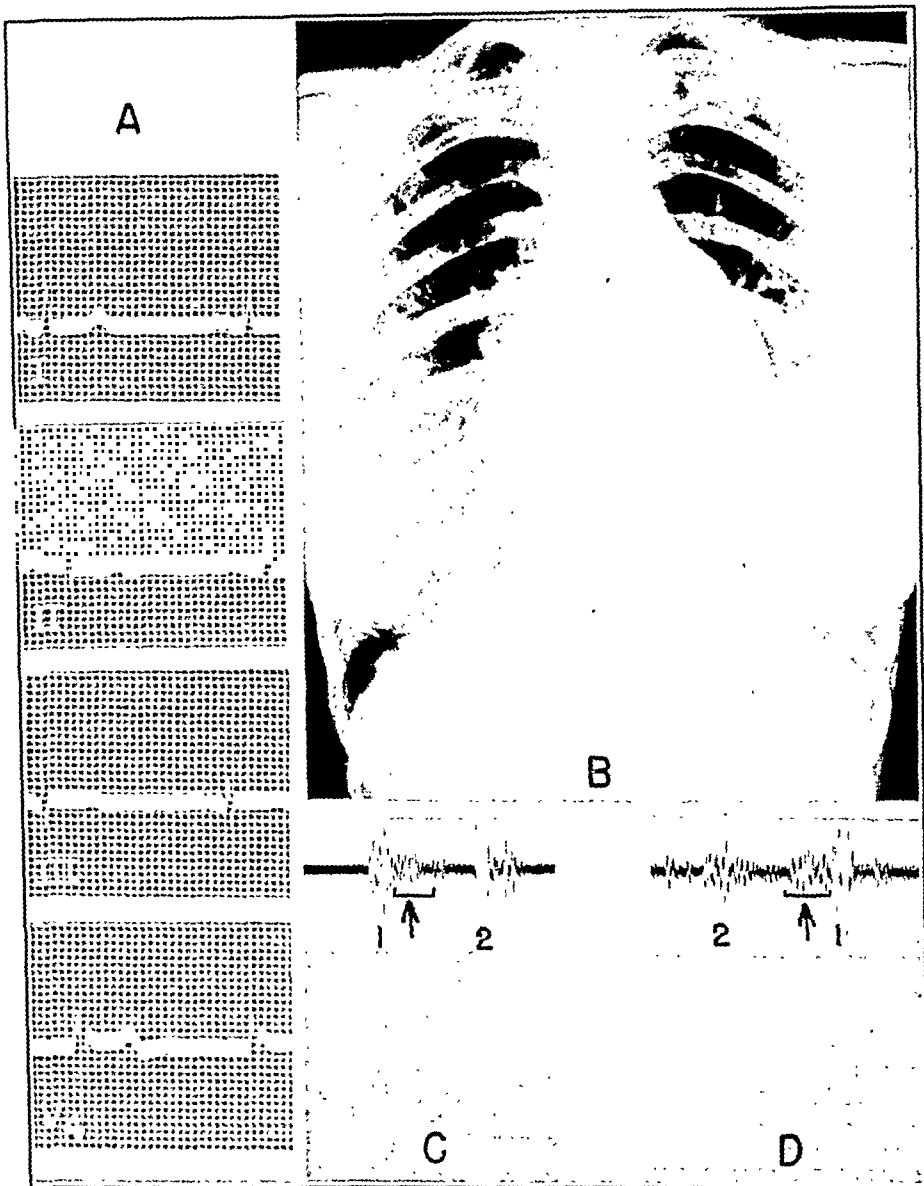


FIG. 1.—(R.D.S.) A. Standard four lead Electrocardiogram. B. Teleoroentgenogram of chest showing configuration and size of heart. C. Phonocardiogram taken over pulmonic area; arrow points to systolic murmur. There is splitting of the pulmonic second sound. D. Phonocardiogram taken over mitral area; arrow points to presystolic murmur. Further description in text.

is no evidence of posterior enlargement of the left ventricle but there is considerable prominence of the right heart anteriorly. Pulsations are very prominent in both hilar regions. No intracardiac calcifications are seen." The impression was "fairly marked enlargement of the right auricle, right ventricle, and both pulmonary arteries, with 'hilar dance.' There is slight enlargement of the left auricle. The findings are rather typical of interauricular septal defect. There is probably an associated mitral stenosis (Lutembacher's syndrome)."

P-A teleoroentgenogram of the chest revealed the transverse diameter of the heart to be 13 centimeters in a chest of 25 centimeters transverse diameter (Fig. 1, B).

**COMMENT:** This patient had cardiac symptoms from early life, with heart disease of an undiagnosed type discovered on the first examination when 10 years old. Two subsequent illnesses were thought to be rheumatic fever. The findings at the present time are typical of interauricular septal defect. To this picture are added the classical physical findings of mitral stenosis. Worthy of emphasis is the fluoroscopic picture of right heart enlargement with tremendous pulmonary dilatation, and pulsating pulmonary vessels as evidenced by a typical "hilar dance."

*Case 2.* C. D., 25 years old, is the oldest of the 5 children. Although not a "blue baby," the mother noted early that the patient seemed listless and nursed poorly. She had considerable difficulty in walking because of "growing pains," not walking until more than 2 years of age. She frequently complained of pain in both thighs and when 3 years old, during an acute episode of leg pain, the mother noted for the first time transient "blueness" of the lips. The family doctor told the mother that the patient had a "bad heart" and "rheumatic fever." When 6 years old the patient recovered rapidly from an attack of pneumonia. Subsequently she attended a school for crippled children for several years because of heart trouble. For 10 years she has had marked shortness of breath even on mild exertion; slight ankle edema appeared 1 year ago and was rapidly relieved by digitalis but with minimal improvement of the dyspnea. At present she is quite limited in her activity, unable to climb stairs even slowly without severe dyspnea. Expo-

sure to moderately cold air leads to marked tingling of her hands and feet.

Physical examination revealed a poorly developed girl appearing several years younger than her stated age. She was not cyanotic. Blood pressure in both arms and legs was 90/70. Positive physical findings were limited to the chest and abdomen. She, like her sister, had a definite precordial bulge of the bony framework of the left chest. Percussion demonstrated enlargement of the heart to both the left and right. There were no thrills present. A moderate systolic murmur was heard in the first interspace to the left of the sternum and the pulmonic second sound was accentuated. On 2 occasions there has been heard a faint blowing, early diastolic murmur in the 1st and 2d left interspaces. An extremely loud, harsh, systolic murmur was present in the 6th and 7th left interspaces over the apex. A short presystolic rumble ending in a loud snapping first heart sound could be heard in the 7th interspace in the anterior axillary line. This murmur was quite localized.

The entire right side of her abdomen was tender, most marked in the right upper quadrant where the liver was felt 2 finger breadths below the costal margin in the mid clavicular line. No ascites was present and there was no ankle edema. Fingers and toes showed no evidence of clubbing.

Urinalysis was completely negative and the blood picture was normal.

The electrocardiogram revealed right axis deviation with high broad P waves.  $P_{1, 2, 3}$  deviation with high broad P waves.  $P_{1, 2, 3}$  varied from 1 to 2 mm. in height and 0.10 to 0.13 seconds in duration. The PR interval was 0.17 seconds in duration. The QRS complexes, ST segments, and T waves were not unusual (Fig. 2, A).

Phonocardiography again confirmed the auscultatory findings in that over the pulmonic area there was recorded a systolic murmur (Fig. 2, C), and over the mitral area a loud systolic murmur and a short presystolic murmur ending in a first heart sound of unusually large amplitude (Fig. 2, D).

Fluoroscopic and radiographic examination of the chest was reported as follows: "In the frontal view the transverse diameter of the heart is markedly increased and the general configuration is globular. There is a tremendous prominence in the region of the pulmonary conus. The aortic knob is practically invisible and leaves little or no imprint on the barium filled esophagus in any view. There is some enlargement in the region of the lower right contour. In the right oblique position there is slight generalized posterior dis-

placement of the barium filled esophagus. The marked prominence in the pulmonary conus region is better visualized. In the left oblique there is marked enlargement of the right heart. The heart overlaps the spine posteriorly even when the patient is almost in the true lateral position. Pulsation of all the cardiac borders is accentuated and there is marked expansile hilar pulsation bilaterally. No intracardiac calcification is seen. Moderately severe pulmonary congestion is present." The impression was "marked enlargement of right ventricle, right auricle, and both pulmonary arteries, with severe pulmonary congestion

and 'hilar dance,' findings quite characteristic of interauricular septal defect."

P-A teleoroentgenogram of the chest revealed the transverse diameter of the heart to be 18.3 cm. in a chest of 24 cm. transverse diameter (Fig. 2, B).

COMMENT: This patient also has had symptoms dating from early life with a defective heart found when 3 years old, during an acute illness considered to be rheumatic fever. It is not clear whether her early symptoms were

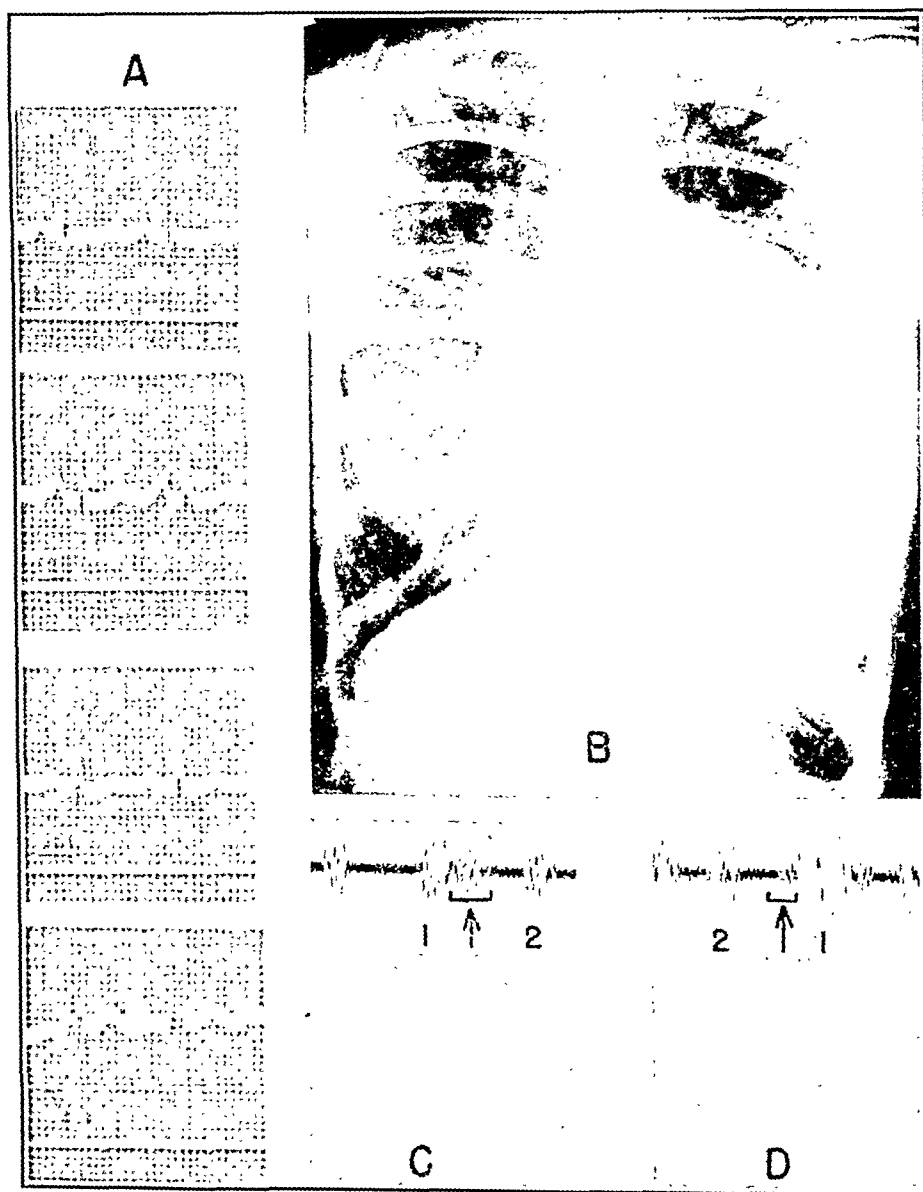


FIG. 2.—(C.D.) A. Standard four lead electrocardiogram. B. Teleoroentgenogram of chest showing configuration and size of heart. C. Phonocardiogram taken over pulmonic area; arrow points to systolic murmur. D. Phonocardiogram taken over mitral area; arrow points to short presystolic murmur. Further description in text.



due to congenital heart disease alone or in combination with rheumatic fever. However, these symptoms have persisted to the present time. Physical examination is suggestive of mitral stenosis, and the fluoroscopic picture is typical of interauricular septal defect in that the right heart is selectively enlarged with a small aorta, and marked prominence of the pulmonary vessels with striking expansile pulsations, so-called "hilar dance." The greater heart size in this case is probably related to a larger interauricular septal defect and more severe mitral stenosis, both factors leading to greater strain on the right heart. Although the diastolic murmur of mitral stenosis is not as loud or as long as in the first case, it is believed that the clinical diagnosis of Lutembacher's syndrome is justified.

**Discussion.** In the literature on Lutembacher's syndrome we have found a total of 54 cases with post mortem description of an interauricular septal defect complicated by mitral stenosis. Lutembacher, presenting the 25th recorded case in 1916<sup>12</sup>, discussed in a lengthy review the etiology and hemodynamics of this association. The syndrome was subsequently given his name. In 4 reviews up to 1944<sup>13,17,26,27</sup>, a total of 52 cases had been collected. Since then there have appeared 2 other reports<sup>7,16</sup>. No reports mentioned a familial occurrence.

The etiology of the mitral stenosis in this syndrome has not been conclusively established. Earlier writers felt that it was congenital in origin, but recent authorities<sup>13,17</sup> believe that when mitral stenosis complicates an interauricular septal defect, it is secondary to endocarditis acquired after birth. Further support for this belief is advanced by the history of rheumatic fever in both of our patients.

There is no constant clinical pattern found in individuals suffering from an interauricular septal defect. In com-

mon with other types of congenital heart disease, retardation of physical and/or mental growth and development is found, such patients usually appearing immature. There is frequently a bulging of the left precordium, the costal cartilages to the left of the sternum bowing convexly. There is also evidence of marked increase in intrapulmonary pressure as indicated by accentuation, or splitting of the pulmonic second sound. Systolic murmurs from the apex to the base have been described. The most common location of the systolic murmur is over the pulmonic area in the first or second interspace to the left of the sternum. Occasionally, there appear diastolic murmurs at the base probably due to relative pulmonic insufficiency.

Since physical examination usually is not clearly diagnostic, much emphasis must be placed upon fluoroscopic examination. In recent years definite criteria for the radiologic diagnosis of interauricular septal defect have been established, first by Assmann<sup>1</sup> and by Dressler and Roesler<sup>4</sup> and more recently by Sussman, *et al.*<sup>24</sup>. This pattern consists of (1) generalized enlargement of the right side of the heart; (2) marked prominence of the pulmonary conus, (3) increased hilar markings, frequently with "hilar dance", (4) small left ventricle, (5) small to hypoplastic aorta. A diagnostic procedure of value in the diagnosis of interauricular septal defect is right heart catheterization. This has been discussed recently<sup>2,3,21</sup>. Unfortunately neither of these sisters has given permission for the performance of this procedure.

For the diagnosis of a superimposed mitral stenosis one must hear the characteristic apical diastolic murmur. It should be emphasized that the mitral stenosis may be "silent," the lesion appearing at autopsy when no murmur was present on clinical examination.

The usual explanation for such "silent" valvular lesions is that coincident to a large auricular septal defect, there is a reduced blood flow through the stenosed mitral valve, insufficient to set up an audible murmur.

To establish the presence of Lutembacher's syndrome it is necessary to rule out mitral stenosis complicated by relative pulmonary insufficiency. Evidence of marked left auricular enlargement is absent in Lutembacher's syndrome, since the defect acts as a safety valve in releasing increased pressure within the left auricle resulting from a stenosed mitral valve.

Other congenital cardiac lesions must be differentiated from interauricular septal defect, alone or in conjunction with mitral stenosis.

Patency of the ductus arteriosus typically shows dilation of the pulmonary conus and often striking pulsations of the hilar vessels of the type described as "hilar dance." In atypical form these findings may be absent and the classical machinery-type murmur may not be present. However, there is usually present a high arterial pulse pressure, and on fluoroscopy the aorta is found to be prominent and pulsating vigorously. When enlargement of the heart is present both ventricles show hypertrophy.

Eisenmenger's complex (interventricular septal defect, dextroposition of the aorta, right ventricular hypertrophy, but with a normal or dilated pulmonary segment, thus differing from the tetralogy of Fallot) is characterized by the presence of cyanosis which appears early in life and persists. Cyanosis in auricular septal defects is at most transient, persisting only as a terminal event.

Uncomplicated interventricular septal defects even if large do not lead to such marked enlargement of the right heart, and vigorously or expansilely pulsating hilar vessels are not seen. Commonly in such cases the only evidence of cardiac abnormality is the characteristic harsh and well localized, systolic murmur and thrill to the left of the mid sternum. Acquired lesions producing dilatation of the pulmonary artery and chronic cor pulmonale must also be excluded.

**Summary.** 1. Familial congenital interauricular septal defect complicated by mitral stenosis (Lutembacher's syndrome) is described apparently for the first time.

2. This disorder was found in 2 sisters aged 21 and 26.

3. The literature concerning familial congenital heart disease has been reviewed.

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# THE PROBABLY GRAVE SIGNIFICANCE OF PREMATURE BEATS OCCURRING IN ANGINA PECTORIS INDUCED BY EFFORT\*

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It is a common experience of clinicians to study patients with subjective symptoms characteristic of Heberden's angina but with few of the physical phenomena of cardio-vascular disease and with electrocardiograms that are either equivocal or essentially normal.

Various techniques have been used by investigators for the primary purpose of recording on the electrocardiogram changes occurring when the elusive symptoms of effort angina are produced either by reducing oxygen pressure in the arterial blood<sup>4</sup> or by increasing cardiac work by graded exercise<sup>6</sup>.

The following procedure has been used in our electrocardiographic laboratory for 8 or more years, and has justified itself in patients who have symptoms of angina pectoris, but whose physical examination and resting electrocardiogram do not give adequate objective data.

The patient is required to exercise only sufficiently to reproduce the subjective symptoms from which he is seeking relief. This exercise procedure is carried out under the close supervision of a trained observer; and its type and duration vary greatly from patient to patient depending upon the exercise tolerance of the individual. Electrocardiograms are made before, during, and after induced attacks of the primary complaint. No accidents have resulted from these studies—though there doubtless could be potential danger if laboratory technicians are per-

mitted to collect such data unsupervised.

For the period of our study the most significant change in the electrocardiograms in attacks of induced angina pectoris has been the occurrence in 4 patients of premature ventricular beats. It must be emphasized that in each case there was normal rhythm before and after the induced episode. The purpose of this report is to evaluate the significance of these observations.

**Case Reports.** CASE 1. H. H., white male, aged 52, occupation, merchant, was seen April 2, 1945, with the major complaint that after active exercise he developed a burning and aching pain under the upper sternum and the upper left arm. With rest, the patient was free of subjective symptoms within a few minutes. He had made the interesting observation that during the attacks his pulse was "too slow" but the rate was normal with rest and with the cessation of substernal pain. His symptoms were of 5 months' duration and were becoming progressively more incapacitating.

Before the development of the present complaint he had been robust and well.

The patient customarily smoked 15 to 20 cigarettes a day and took a drink of whiskey before lunch and 2 drinks before dinner.

**Physical examination:** The patient was a robust man, well developed and nourished. Ht. 5' 10", wgt. 188 lbs. His general examination showed him to be essentially normal. The heart was normal in size; the rate was 80 and rhythm was regular. The first sounds were normal and there were no murmurs. The pulmonic second sound was normal in intensity and quality and the aortic second sound was moderately accentuated and amphoric in quality. The peripheral arteries were normal in texture. The blood pressure was systolic 145, diastolic 90.

\* Presented in abstract at the 61st meeting of The Association of American Physicians at Atlantic City, May 1948.

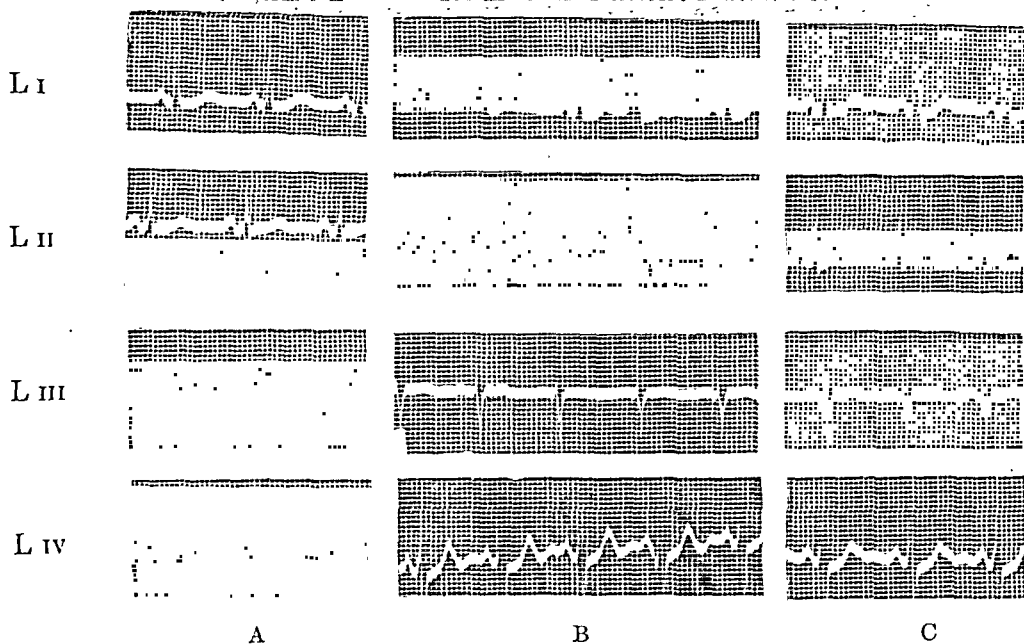


FIG. 1.—Case 1. (H.H.) A. *Before exercise*: regular rhythm, rate 80, PR 0.15, QRS 0.06, moderate left axis deviation, slight ( $\frac{1}{2}$  mm.) depression of S-T in IV, notched T. B. *During an attack following exercise*: Bigeminal rhythm, rate 100 in Leads I and II, normal sinus rhythm, rate 95, in Leads III and IV, PR 0.14, QRS 0.06, moderate left axis deviation,  $\frac{1}{2}$  mm. depression S-T I and II. C. *Exercise after 0.6 gm. quinidine sulphate*: normal sinus rhythm, rate 90, PR 0.14, QRS 0.06, moderate left axis deviation,  $\frac{1}{2}$  mm. depression S-T in I and II and 1 mm. depression ST4—T3, slightly more positive. No symptoms suggestive of angina pectoris.

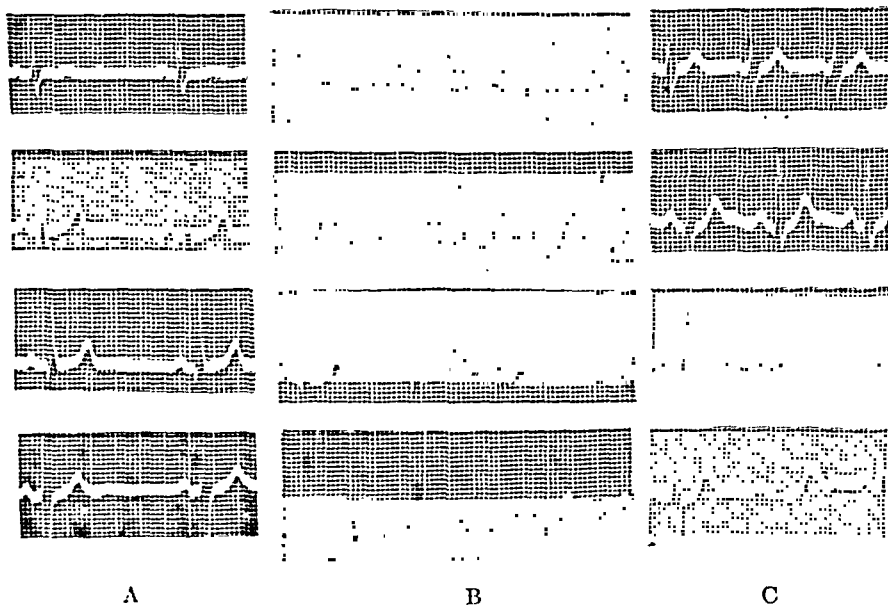


FIG. 2.—Case 2. (T.A.) A. *Before exercise*: normal sinus rhythm, rate 50, PR 0.16, QRS 0.09, moderate R, small slurred S, low T in I, small Q, high R, high T in II and III, moderate R and S, upright T in IV. "U" waves present in I, II, and IV. B. *During an attack following exercise*: Lead I—normal sinus rhythm, rate 70—T wave slightly higher, Leads II and III—frequent ventricular premature beats, Lead IV—1 mm. depression of S-T—T waves diphasic ( $\pm$ ). C. *Exercise after 0.6 gm. of quinidine sulphate*: normal sinus rhythm, rate 90 in I and II, rate 73 in III and IV, PR 0.16, QRS 0.10, moderate R, moderate S, high T. in I, high R, moderate S in II, slightly less positive T and prominent "U" in III, prominent "U" wave in IV, no symptoms suggestive of angina pectoris.

All laboratory findings were negative.

*Roentgen-ray report:* "The heart is normal in size and shape. Cardiothoracic ration is 48%. There is some increased density of the aorta. The esophagus is normal and there is no herniation."

*Electrocardiograms* are shown in Fig. 1.

This patient was able to be entirely free from symptoms while he was taking quinidine 0.3 gm., 3 times a day at 10 a. m., 4 p. m., and 8 p. m. On November 5, 1945, he suffered a coronary occlusion which proved fatal in about 2 hours after the beginning of the attack.

No information is available as to whether he was taking quinidine regularly before the fatal episode. His physician thought he was not.

CASE 2. T.A., white male, aged 56, occupation, farmer, was seen May 3, 1946, whose chief and only complaint was burning pain, substernal in location, induced by effort and relieved by rest. The attack was most likely to occur after meals. If he did not stop and rest he would get an aching pain in both shoulders and in the upper left arm. The patient felt that his symptoms were due to "indigestion." He did not smoke or use alcohol. His history otherwise was significantly negative.

*Physical examination:* The patient was a well developed and well nourished man who

was obviously apprehensive, but did not appear ill. The only abnormal findings were localized in the cardiovascular system. The heart was normal in size and shape. There were no murmurs. The pulmonic second sound was normal in intensity and quality. The aortic second sound was amphoric in quality and increased in intensity. Heart rate was 56 per min. and rhythmic. Blood pressure was 165 systolic, 110 diastolic.

*Electrocardiogram:* Fig. 2.

Due to the control of the premature beats by quinidine and a marked increase in exercise tolerance, quinidine sulphate 0.3 gms. was prescribed to be taken 3 times a day. The patient continued this medication for 2 weeks with a marked improvement in exercise tolerance. The quinidine sulphate was discontinued by his family physician because the patient developed gastric symptoms which he attributed to the drug. The physician states that the patient has retired from work on account of the cardiac disability. He is now using nitroglycerine frequently for the relief of pain. The patient has not been re-examined by me since the original consultation.

CASE 3. J.B.B., white male, aged 44 occupation, oil company executive, was seen January 1, 1946, with the chief complaint of a "squeezing pain" beginning under the sternum with radiation to both arms. At times

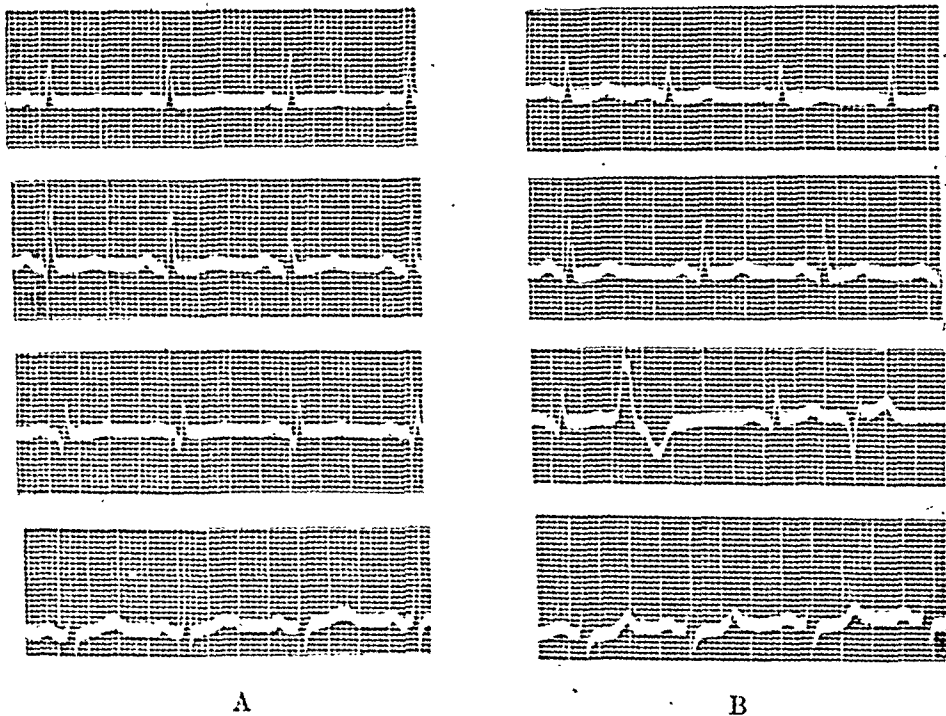


FIG. 3.—Case 3. (J.B.B.) Before exercise: normal sinus rhythm, rate 85, PR 0.16, QRS 0.08, small Q in II and III, low T in I, II and III—low notched T in IV. During an attack following exercise: normal sinus rhythm, rate 85 in Lead I, rate 75 in Leads II, III, and IV, interrupted by premature beats from multiple foci in Lead III, PR 0.16, slight (1 mm.) depression of S-T and more "peaked" T in IV, T waves in all leads more positive.

it extends through to the area of the left scapula. The symptoms are consistently precipitated by exercise and there is prompt relief with rest. The symptoms began 3 months previously and were becoming increasingly more incapacitating.

There is nothing else of significance in his past or family history except that his father died at the age of 64 from a "heart attack".

Physical examination showed the patient to be normal with a blood pressure of 130 systolic and 85 diastolic.

The *electrocardiograms* are shown in Fig. 3.

Since the original study his clinical course has been unsatisfactory. Quinidine 0.3 gms. 3 times a day apparently increase his exercise tolerance but not significantly. His physician reports "his exercise tolerance has progressively lessened and he now uses nitroglycerine frequently. He has not had symptoms characteristic of acute coronary occlusion".

CASE 4. T.O.C., white male, aged 63, physician, was seen October 18, 1944, with the chief complaint of severe substernal pain with radiation to both arms induced by minor physical effort and promptly relieved by rest. He was impressed by the pounding of his heart during the attacks of pain and by the irregularity of the pulse. On numerous occa-

sions he had taken nitroglycerine with prompt relief. The present complaint began approximately 16 months previous to examination and had become increasingly more severe.

The patient described himself as being otherwise quite well; however, he had known for "many years" that his blood pressure was elevated.

*Physical examination:* a well developed, well nourished male, apparently somewhat apprehensive, age 63. Ht. 5'9", weight 187 pounds. His general examination was not remarkable except for the cardiovascular system. The heart was moderately enlarged to the left. The apex beat was forceful and located in the nipple line, 5th intercostal space. The first sound was normal in quality. There was a slightly harsh systolic murmur heard over the aorta in the first and second right intercostal area. The aortic second sound was markedly accentuated and grossly amphoric in quality. The pulmonic second sound was essentially normal. Heart rate was 78 and rhythmic.

There were signs of a moderate generalized arteriosclerosis. The blood pressure was systolic 190, diastolic 105. Pulse rate was 78 and rhythmic. Roentgen-ray of the heart: "The heart is enlarged, particularly the left

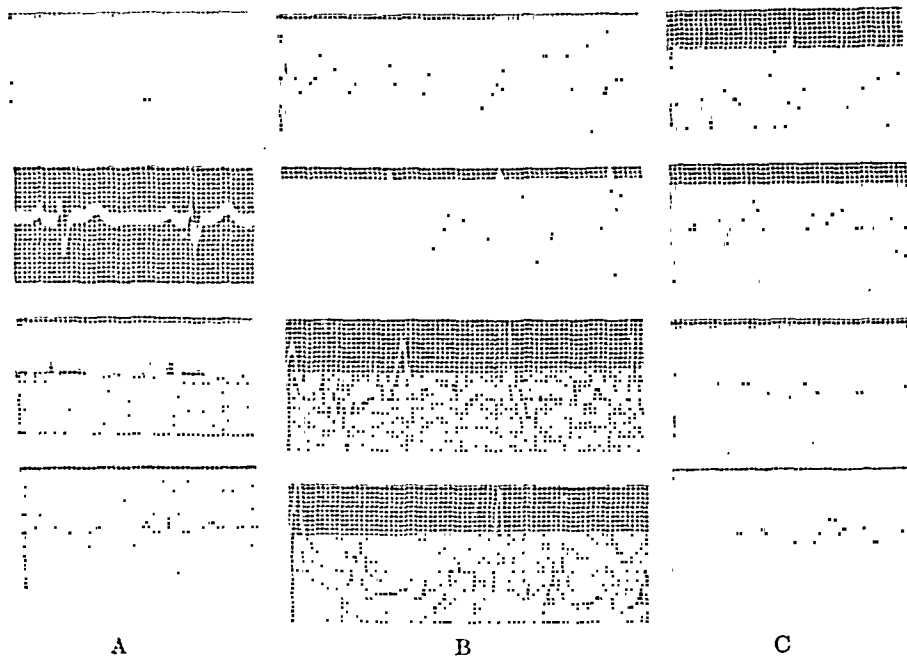


FIG. 4.—Case 4. (T.O.C.) *Before exercise:* normal sinus rhythm, rate 65, PR 0.20, QRS 0.10, high R, moderate S in I, small R, deep slurred S in II, small R, deep S, small R1, small S1 in III. *During attack following moderate exercise:* throughout tracing there is a basic sinus tachycardia, 120 in Lead I, gradually slowing to 105 in Lead IV, frequent ventricular extrasystoles, producing a bigeminal rhythm for the most part. Moderate depression of S-T intervals in Leads I, II, and IV. *Exercise after 0.6 gm. quinidine sulphate:* normal sinus rhythm, rate 85, same as control except—slightly depressed S-T in I, slight elevation of S-T and higher T in II and III, slight depression (1½ mm.) and sagging of S-T and diphasic T in IV.

ventricle. The aorta is moderately dilated and the density increased, indicating arteriosclerosis. The cardio-thoracic ratio is 52%."

The *electrocardiograms* are shown in Fig. 4.

This patient was warned as to the dangers of exercise and advised to reduce his weight by 10 pounds. Reduction in the amount of work was recommended. Quinidine sulphate 0.3 gm. was prescribed at 10 a. m., 4 p. m., and 8 p. m. He felt that this medication improved his exercise tolerance about 50% and he was particularly impressed with the absence of cardiac pounding when an attack was precipitated by effort beyond his physical tolerance.

After omitting the quinidine for approximately 1 week, he endeavored to rescue his granddaughter from a main highway when he saw an approaching motor car bearing down upon her. The child saved herself; but he was seen to fall forward just before reaching the highway, death obviously occurring instantaneously.

**Discussion.** In the practice of cardiology premature beats *per se* are not regarded as important<sup>5,11</sup>. To this generally accepted fact there are few exceptions, but these exceptions may be of peculiar significance.

Extrasystoles, as a general rule, are increased during the post-acceleration or slowing period following induced tachycardia.

In the patients under discussion premature beats occurred during the period of acceleration and at the peak of chest pain, and disappeared with rest and cardiac slowing. It is also significant that the rhythm was normal except during the induced episodes; and that 3 of the patients, Cases 1, 2, and 4, noted an irregular pulse and "heart pounding" during attacks of substernal pain induced by the exercise of daily routine.

Bourne,<sup>2,3</sup> studying the effects of exercise on the frequency of premature beats, found that in rheumatic heart disease no significant effect resulted from exercise, while in 11 patients with arteriosclerosis 9 showed a significant increase in the number of extrasystoles during the post-acceleration period following exercise. He felt that the ex-

planation for an increased number of extrasystoles in this group with vascular disease was to be found in the effects of exercise in the production of local anoxemia resulting from disease in some branch of a coronary artery.

The opinion expressed by Wood and Wolferth<sup>12</sup> that the majority of attacks of angina pectoris are associated with a localized circulatory disturbance in the myocardium is tenable. This hypothesis does not imply that the main stem and branches of the coronary arteries are not narrowed, but that some branches are relatively more involved than others. The areas supplied by these lesser vessels suffer a greater degree of anoxemia during the period of increased metabolic demand resulting from exercise. It may be assumed that in the patients now under discussion, a common factor operated in producing the subjective symptoms and the premature beats and that this factor became operative following exercise. With rest, pain subsided, and the extrasystoles disappeared, which strongly suggests that both resulted from a local anoxemia of the myocardium.

In Cases 1 and 2 there appeared to be a definite relationship between the premature beats and exercise tolerance. Both patients, after therapeutic dosage of quinidine sulphate, tolerated 3 or 4 times the amount of exercise without occurrence of premature beats and with no reproduction of the original subjective symptoms. Explanation of this observed fact is not simple but it is suggested that either quinidine increased the tolerance of the heart muscle to oxygen want or that frequent premature beats reduced the minute volume flow through the coronary circulation. Case 1 is significant in this connection. The patient was observed frequently up to within a few weeks of the time he



had a fatal coronary occlusion, and he was essentially free from symptoms while he continued the use of quinidine, which he thought kept his pulse regular and at a normal rate. Case 4, a physician, felt that quinidine definitely reduced the severity of the attacks of angina and he attributed to the use of this drug the relief of the irregularity and pounding of his heart noted previously.

One of the unhappy end points of angina pectoris is sudden death and this catastrophe all too frequently occurs when patients exercise beyond their tolerance. Sudden death under these circumstances probably results from fibrillation of the ventricle. Robinson and Hermann and others<sup>6,10</sup> have shown the relationship of paroxysmal ventricular tachycardia to ventricular fibrillation and the importance of coronary artery insufficiency in the production of these grave ventricular rhythms. A bigeminal rhythm after acute myocardial infarction may precede ventricular tachycardia and fibrillation, both in the experimental ligation of a coronary artery and in acute coronary occlusion occurring in man. It is with these facts in mind that one feels justified in suggesting that the occurrence of frequent premature beats and especially a bigeminal ventricular rhythm during an attack of induced angina pectoris has grave prognostic significance.

Case 4 again emphasizes the dangers inherent in excessive exercise in angina of effort. It is thought that exercise during an attack of pain is peculiarly hazardous for patients with the type of disturbed rhythm under discussion.

In 1924<sup>7</sup> the writer suggested that quinidine sulphate controlled ventricular tachycardia complicating acute myocardial infarction. In 1934<sup>8</sup> after more extended experience, the writer advocated quinidine sulphate as the

most potent drug to prevent development of paroxysmal ventricular tachycardia and fibrillation during the first week following acute myocardial infarction. Since 1934 it has been our routine policy to use 0.3 gm. of this drug 3 times a day at 4-hour intervals as a preventive agent. A review of our clinical material strongly indicates that the practice has much merit.

Borg<sup>1</sup> in 1939 presented unequivocal evidence that quinidine sulphate in conservative doses lessened post-infarction irritability of the ventricle and employed its use in acute coronary occlusion.

It is logical, therefore, that quinidine sulphate be prescribed in therapeutic doses for prophylaxis against ventricular fibrillation and sudden death in patients who have frequent premature ventricular beats at the peak of effort angina: and in some cases the intensity of the attacks of pain is lessened and exercise tolerance increased by depression of the irritable myocardium resulting from a factor or factors common to the mechanism of pain and disturbed rhythm.

**Conclusions:** 1. It is obvious that these 4 patients, selected from many, were victims of the angina pectoris of effort. With the exception of Case 4 they had few signs of cardiovascular disease and resting electrocardiograms were equivocal in all 4.

2. Premature beats occurring at the peak of induced angina and cardiac acceleration were the most significant change in the electrocardiogram. The ectopic beats and pain disappeared with rest and cardiac slowing.

3. In 2 of the patients exercise tolerance was greatly increased by quinidine sulphate which prevented the occurrence of premature beats with effort.

4. It is suggested that the occurrence of premature beats, especially pulsus bigeminus in an episode of ef-

fort angina may have grave prognostic significance. It is, however, obligatory that a larger series of patients be studied before final conclusions can be drawn.

5. Quinidine sulphate can profitably

be used in the type of patients under discussion. The dose must be conservative, 0.2 to 0.4 gm., 3 times daily equally spaced during the period of physical activity.

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# THE INSENSIBLE LOSS OF WATER IN CONGESTIVE HEART FAILURE\*

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Congestive heart failure is characterized by a marked disturbance in fluid balance. While the failure of the kidneys to excrete water (and salt) in this condition has been extensively studied, water loss by other routes has been less thoroughly investigated. It is the purpose of this report to measure this loss and discover possible theoretical and practical conclusions.

In this discussion the term "insensible perspiration" will be used to describe the water loss through the skin occurring under conditions in which the thermal stimulus to sweating is absent. This term has been defined somewhat differently by some other workers, having been used to express (in the absence of sensible sweating), (1) the total weight loss of the body, or (2) the total water loss from both lungs and skin. It seems more logical to reserve the term "perspiration" for a function of the skin. Without sensible sweating the normal body continually loses weight from 3 sources: (1) from expired water vapor, (2) from excess weight of expired  $\text{CO}_2$  over absorbed  $\text{O}_2$ , and (3) from water loss through the skin. The last component has been reported as varying from 167 to 1700 gm. per day<sup>14</sup> but the most careful measurements on normal individuals (Benedict

and Benedict,<sup>1</sup> Burch and Winsor<sup>9</sup>) have shown that it averages 14 gm. per hour with extremes of 8 and 21 gm., and that it comprises about 50% of the total insensible weight loss.

The total insensible water loss has been roughly correlated with the metabolism (Benedict and Root<sup>2</sup>), and has been found to furnish a fairly constant percentage of body heat loss (Soderstrom and Dubois<sup>25</sup>). Individual variations over short periods are large, however, (Wiley and Newburgh<sup>27</sup>) and it is not clear how much of the increased loss with higher metabolism is due simply to increased loss via the lungs. It is well established that water (and therefore heat) loss via the lungs is related closely to the pulmonary ventilation (Galeotti,<sup>12</sup> Burch<sup>3,4,5</sup>) and probably to nothing else.

Insensible perspiration, even when used in its simpler restricted sense is not due to a single process. While the bulk of the water loss is presumably a diffusion and evaporation through the intact skin not involving sweat gland activity<sup>19,21,26</sup> nevertheless a small portion will be included as a result of palmar and solar sweating, the sweat glands of these areas functioning continuously and being under various non-thermal controls. The mechanism of

\* This research was aided by a grant to Columbia University from the Baruch Committee on Physical Medicine.

water loss through the non-sweating skin has not been wholly clarified. The most plausible picture is that of a diffusion through the deeper layers and an evaporation through the cornified layers. This is roughly the explanation offered by Winsor and Burch<sup>7,8</sup> who found comparable rates of water transfer through dead and living skin. If this is true the rate of water loss should be determined by simple physical factors such as skin temperature and vapor pressure of intradermal water. Ray and Burch<sup>23</sup> regard intravascular hydrostatic pressure as unimportant with reference to the rate of diffusion of water through the skin.

Congestive heart failure with edema, associated with severe derangement of peripheral circulation, and distortion of normal skin fluid relationships presents a situation in which the hypotheses of water transfer through the skin as well as the practical importance of this means of water elimination may be tested. Soderstrom and Dubois<sup>25</sup> suggested from examination of their measurements of total insensible water loss in congestive failure that possibly the portion from the skin was diminished. Zak and colleagues<sup>28,29</sup> in a series of reports beginning in 1929 found markedly reduced and even negative figures for insensible weight loss. Several workers<sup>11,14,15,17,20</sup> have failed fully to confirm these findings. None, however, has partitioned the weight loss between the skin and lungs. Kauf and Zak's observation of localized diminished sweating in congestive failure<sup>16</sup> was made on the palms, which, as mentioned previously, have sweat glands under specialized controls. Burch<sup>6</sup> measured the water loss from localized areas in patients in congestive failure and clearly demonstrated a lower than normal sweating response to a hot environment. His figures, however, do not show a clear-cut difference between

normal subjects and cardiac patients in a cool environment.

The possibilities, therefore, remain that insensible perspiration in congestive heart failure is unchanged, impaired, or enhanced. Perhaps our theories of simple diffusion and evaporation are complicated by varying affinities of the tissue for water. Perhaps, in spite of the negative evidence, the transfer of water is carried on in part by some active process in the cells of the skin. It is the purpose of this report to re-examine the problem, partitioning in 14 experiments (8 of them on patients with congestive heart failure), the insensible weight loss into the various components mentioned above.

**Method.** Five subjects studied were patients in severe cardiac decompensation, the degree of right-sided congestive failure being predominant. They all had pitting edema of the extremities and elevated venous pressures. Three of these patients were restudied after cardiac recompensation had taken place, making a total of 8 experiments on patients with heart disease. In addition, 6 experiments were carried out on 4 patients with an illness having no significant cardiac component, in order to afford a broader basis for comparison of the results both within the series and with those of other observers. This made the total number of experiments 14.

All studies were carried out in a room, the temperature and relative humidity of which could be kept constant throughout each experiment and from experiment to experiment. With the exceptions noted in Table 1, all experiments were carried out in room temperatures close to 23° C. and relative humidities of 51%. No attempt was made throughout the course of the experiment to keep the patient under basal conditions. It was desired to simulate the typical daytime activity of the patient at bed-rest. In practical terms this meant that the subject lay quietly under a light covering, activity being confined to something such as reading.

The procedure in each experiment involved the steps outlined in the following numbered paragraphs:

1. Total weight loss per unit of time was established by weighing the subject over a period of hours, usually 3 or 4, on a "silk" platform scales accurate to the nearest 7 gms. Any excreta were also weighed. Clothing, limited to a light hospital gown, was kept unchanged. To minimize the error due to adsorption of water on the clothing a 45-minute period before the initial weighing was allowed for equilibrium with the environment to take place.

2. On 2 occasions during each experiment the expired air of the subject was collected for 10 minutes in a Douglas bag, using the usual mouth-piece, noseclip, T-tube, flutter valves and connecting tubing. Loss of water through the respiratory tract was calculated from the ventilation figures so obtained, as follows:

nique in 1912 by Galeotti<sup>12</sup> and more recently by Burch,<sup>3</sup> which were 37 and 33 mm. Hg. respectively, for the vapor pressure. The accuracy of the assumption is unimportant for comparative results, so it is not necessary to decide which value is the most likely accurate one. Hyperpnea lowers the vapor pressure of water in the expired air only very slightly during voluntary overbreathing (Christie and Loomis<sup>10</sup>), and in dyspneic patients (Burch<sup>4,5</sup>). The relative humidity, and thence the vapor pressure of the inspired air, was determined from readings on a sling psychrometer every 30 minutes.

3. Analyses of the expired air collected during the two 10-minute periods were made on the Haldane apparatus, and from these the weights of carbon dioxide expired and oxygen consumed were calculated. The difference between these two weights may be labelled the "metabolic weight loss." The gas analyses on the two periods of

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Resp. water loss =  $\text{H}_2\text{O}$  expired air —  $\text{H}_2\text{O}$  inspired air

$$\text{H}_2\text{O ins. air Gm./hr.} = \frac{\text{V.P. ins. air}}{\text{B.P.} - \text{V.P. insp. air}} \times \frac{18}{22.4} \times \text{Vent. (Insp.) in L./min. S.T.P.} \times 60$$

$$\text{H}_2\text{O exp. air Gm./hr.} = \frac{\text{V.P. exp. air}}{\text{B.P.} - \text{V.P. exp. air}} \times \frac{18}{22.4} \times \text{Vent. (Exp.) in L./min. S.T.P.} \times 60$$

V.P. = vapor pressure of water  
B.P. = barometric pressure

S.T.P. = standard temperature and pressure (0° C., 760 mm. Hg., dry)

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The vapor pressure of expired air was assumed to be 44 mm. of Hg. in all the experiments. This figure is slightly lower than that found by Christie and Loomis<sup>10</sup> to be the vapor pressure of alveolar air and was so chosen to compensate for the lower vapor pressure they found in dead space air. These figures for the water in expired air are considerably higher than those found by a different tech-

collection did not differ greatly, the average probably being representative of  $\text{CO}_2$  excretion and  $\text{O}_2$  consumption over the entire course of the experiment.

4. Skin temperatures were measured from 10 different body regions by the thermocouple-potentiometer method at 30-minute intervals. Each skin region was weighted according to the percentage of body surface represented

(Hardy, and Dubois, modified<sup>13,21</sup>), and an average skin temperature obtained. When the average skin temperature was less than 34° C. (cf. Kuno) any weight loss due to sensible perspiration was deemed unlikely.

5. As an additional check on the possibility of sensible perspiration a gauze sponge was placed on the abdomen under an airtight plastic seal covering six square inches. This was kept in place throughout the experiment, being weighed before placing it and after removal. If the weight gain of the sponge was less than 0.050 gm./6 sq.in./hr. (an arbitrarily chosen

figure) sensible perspiration was assumed to be minimal.

6. Determination of the insensible perspiration by weight studies will obviously include the amount of palmar and solar sweat produced. An estimate of the magnitude of this palmar and solar perspiration was obtained by the technique described above, a sponge being placed on one palm of each subject. The perspiration obtained in this manner was analyzed for chloride content, being recorded as sodium chloride.

**Results.** The results of the experiments are recorded in Table 1. There

TABLE 1. SUMMARY OF MEASUREMENTS OF INSENSIBLE WEIGHT LOSS AND ITS SUBDIVISIONS IN 14 EXPERIMENTS ON CARDIAC PATIENTS AND OTHERS

Experiment number	Patient	Date	Diagnosis	Total weight loss: Gm./hr.	Metabolic loss: Gm./hr.	Water loss via lungs: Gm./hr.	Skin loss: Gm./hr.	Palmar sweat: Gm./hr./6 sq. in.	Palmar sweat NaCl meq./l.	Abdominal sweat: Gm./hr./6 sq. in.	Mean weighted skin temp. °C.	Rectal temp. °F.	Approx. weight of patient
1**	W.J.	2/18/47	Arteriosclerotic heart disease V.P. 175***	61	5.3	25.6	30.1	0.040	16	0.025	33.2	98.5	155
2†	W.J.	3/5/47	V.P. 80	39	3.9	19.0	16.1	0.030	36	0.020	32.6	99.4	110
3	J.B.	3/21/47	Arteriosclerotic heart disease V.P. 185	45	1.4	19.7	23.9	0.030	35	0.050	32.0	97.0*	170
4	J.B.	4/1/47	V.P. 78	40	2.6	17.2	20.2	0.030	18	0.055	32.4	97.7*	140
5	C.J.	4/22/47	Hypertensive disease V.P. 130	57	6.1	13.8	36.9	0.085	21	0.081	32.5	98.2	155
6	C.J.	5/15/47	V.P. 110	53	4.9	10.7	37.4	0.075	19	0.074	33.0	99.5	130
7	M.K.	3/31/47	Arteriosclerotic heart disease V.P. 175	43	2.0	19.8	21.2	0.060	58	0.012	34.3	99.6	160
8	H.G.	10/21/46	Rheumatic heart disease V.P. 245	42	2.4	19.0	20.6	0.025	12	0.017	31.6	99.8	140
9§	E.H.	5/1/47	Nephritis nephrotic phase	54	2.5	14.6	36.9	0.050	29	0.030	33.7	99.1	190
10	B.H.	10/7/46	Hypertensive disease—Asymptomatic	18	1.7	10.0	6.3	0.030	27	0.003	32.4	99.6	125
11	B.H.	10/9/46	Hypertensive disease—Asymptomatic	21	2.2	11.1	7.9	0.025	11	0.001	33.2	99.6	125
12	M.L.	10/14/46	?G.I. neoplasm	28	1.8	12.7	13.5	0.070	19	0.001	32.6	99.2	110
13	M.L.	10/16/46	?G.I. neoplasm	30	1.8	13.0	13.7	0.090	32	0.002	33.9	99.7	110
14	C.H.	4/10/47	Hypoadrenalism hypothyroidism	35	2.6	9.7	22.7	0.021	40	0.020	30.5	99.6	175

\*\* relative humidity = 38

† relative humidity = 44

§ relative humidity = 57  
temp. room air = 77.1° F.

\* Oral temperature.

\*\*\*V.P. = Venous Pressure in mm. H<sub>2</sub>O

is evidence of frank sweating only in experiments 5 and 6, the abdominal sweat being 0.081 and 0.074 gm./6 sq. in./hr., respectively, even though the skin temperatures were below 34° C. In both experiments the error produced is in the same direction and of the same magnitude so that, while the absolute values for the insensible perspiration are probably somewhat high, they can, nevertheless, be validly compared.

Experiments 1 to 6 are pairs of experiments on 3 cardiac subjects, the first of each pair being during severe congestive failure, the second after recovery of compensation.

In subjects J. B. and C. J. (experiments 3, 4, 5 and 6) the insensible perspiration is essentially the same in both cardiac compensation and decompensation. Subjects M. K. and H. C. (experiments 7 and 8) were tested only during cardiac decompensation, but their values for insensible perspiration are within the range shown by J. B. and C. J.

Subject W. J. (experiments 1 and 2) showed a lowered insensible water loss from the skin when in cardiac compensation—16.1 gm./hr. as compared with 30.1 gm./hr. in cardiac decompensation. This is inconsistent with the findings in experiments 3 to 8 inclusive, and not readily explainable. Both experiments 1 and 2 appeared technically satisfactory, although it is not impossible that an error was made. It may be that this single discrepancy in the evidence for unchanged insensible perspiration, whether cardiac compensation or decompensation is present, reflects an unpredictable variation in the insensible water loss of any individual, *i.e.*, the insensible water loss may vary not only from individual to individual but also in the same individual at different times.

Comparison of the values found for patients with heart disease with the

results in the few patients having other illnesses (experiments 9 to 14), while too few to be conclusive, nevertheless shows no striking differences. An individual variation was expected; all values fell within the range for normal subjects as quoted by Kuno.<sup>18</sup> In a rough way, the insensible water loss is correlated to the size of the patient, but an exact correlation with metabolism could not be expected from a short series, as pointed out by Wiley and Newburgh.<sup>27</sup>

Throughout the entire series of experiments the palmar sweat showed considerable individual variation both in amount and chloride content. While independent of thermal stimuli, indeterminable factors such as mental stress, modify its production. So little is known concerning the factors involved that no certain deductions may be made from the data obtained; there is no discernible evidence, however, of any constant trend in the various disease states studied.

To obtain some idea of the magnitude of the palmar and solar sweat it was assumed that the sweat obtained from one palm was equivalent to one-twelfth of the total. In experiment 1, therefore, the total palmar and solar sweat is 0.5 gm./hr. This represents less than 1% of the total insensible water loss. In experiment 13 the palmar and solar sweat represents 3.5% of the total, and in any of the experiments it can be shown by this crude estimation to be less than 5% of the total insensible water loss. Under different experimental conditions, however, it is entirely possible that the palmar and solar water loss would be of a different order of magnitude.

From the data obtained in these experiments it can be concluded that the changes in circulatory dynamics associated with cardiac failure have no measurable effect on the production

of insensible perspiration. It may be inferred, therefore, that hydrostatic pressure plays no decisive part in the production of insensible perspiration. (It might also be inferred that the cell membrane at the body surface is characteristically impermeable to water in the liquid phase.) It is not possible from examination of the data to decide if the vapor pressure of water acts alone or in combination with an ill-defined secretory function of the cell to produce insensible perspiration; however, its production can be satisfactorily explained by water vapor pressure alone. Further experiments should be devised to test this hypothesis.

In conformity with previous reports on overall insensible water loss, there appears to be a fairly constant value for insensible perspiration from the skin only, for each individual. This individual variation probably is related to surface area. The constancy, regardless of the state of cardiac compensation, excludes this route as a significant source of water retention in cardiac failure. Thus, this report adds to the list of those failing to confirm the small or negative insensible perspiration reported by Zak.

It is agreed (see Peters and Van Slyke<sup>22</sup>) that the insensible weight loss offers at most only a crude index of metabolic rate. Thus the finding (experiment 14) of a rate in the middle of the normal range on a patient with hypothyroidism and hypoadrenalism (BMR-35%) is perhaps not surprising as an isolated example. It is worth noting, however, that the loss via the

lungs was the smallest in the series. Similarly a case of frank hyperthyroidism (not on table) had a total weight loss of only 43 gm. per hour, but of this 20 was water via the lungs and only 19 via the skin. It is certainly within the realm of possibility that the reported correlation of insensible weight loss to the metabolic rate is only an indirect mirroring of the known correlation of the metabolism and the ventilation.

**Conclusions.** Fourteen determinations of the insensible weight loss, partitioned into its several parts were accomplished. Eight of these were carried out on patients with heart disease, including 3 comparisons of the same patient before and after recovery from severe decompensation. From these measurements the quantity of insensible perspiration was found not to change significantly when the circulatory status of an individual is altered by cardiac decompensation, although the amount lost by way of the lungs followed the pulmonary ventilation.

The absolute quantity of insensible perspiration (skin) in these patients and a few others with various diseases correlates only very roughly with body size, and seems to be characteristic of the individual. The range of individual measurements is large but well within the reported range in all instances. The palmar sweat secretion, and by inference, the solar, together contributed little to the total insensible water loss under the conditions of the study, being less than 5% of the

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# THE USE OF ACETYLCHOLINE IN THE OBJECTIVE DETERMINATION OF CIRCULATION TIME IN MAN

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In the course of study of the effects of acetylcholine, it was noted that acetylcholine can give an accurate objective determination of the circulation time in unanesthetized normal dogs and in anesthetized open-chested animals<sup>12,13</sup>. It was shown that acetylcholine yields a distinctly shorter circulation time, shows less variations and appears superior to most methods applicable to animals. It is simple, accurate, and consistent, and an unequivocal end point can be determined electrocardiographically.

In the present report we are presenting results on the use of acetylcholine in the determination of circulation time in man.

**Methods.** The patients were placed in the recumbent position and acetylcholine chloride, in doses of 10 to 60 mg. (0.2 to 1.2 cc. of a 5% solution) was rapidly injected into one of the antecubital veins. Due to the small volume, injection took only a fraction of a second. A double stopcock was used to prevent a premature mixture of blood and acetylcholine inasmuch as blood cholinesterase rapidly destroys acetylcholine. A continuous electrocardiogram on a direct writing Sanborn machine, was taken to record the end point. Time of injection was indicated on the record by simultaneous depression of the lead marker. The circulation time was measured from the onset of injection up to the time an expected auricular or ventricular response failed to occur on time.

Blood pressures were taken before and 1 to

10 minutes after injection. When a blood pressure drop was found multiple readings were taken until the blood pressure returned to the pre-injection level. A syringe with atropine sulfate solution (grains 1/50) was available for intravenous use in case of a prolonged asystole. In this series it was not necessary to employ the atropine.

In most cases, 20 mg. was used initially. If this resulted in no response the dose was increased by increments of 10 mg. but at no time was a dose of more than 60 mg. used. Thus the patients received from 1 to 4 injections.

**Results.** The data was obtained on 37 unselected patients, 21 males and 16 females from the wards and clinics of the Michael Reese Hospital. The age ranged from 17 to 75 years, the average being 53 years. A variety of clinical conditions was present in these patients. Twenty-nine patients responded to one or more injections (Table 1), 8 failed to show any response. Some variation in response was observed. In 6 patients increasing the dose of acetylcholine resulted in a circulation time measurement. In several patients fluctuations in the dose which gave a response were observed. A total of 58 injections were given to the 29 patients who responded, of which 46 were successful in producing a measurable circulation time. In Table 2 is shown the number of responses obtained with the different doses of acetylcholine.

In 20 instances an asystole was observed, varying in duration from 0.9 to 3.8 seconds, with an average of 1.7 seconds. In the other 26 instances no asystole occurred, but a prolongation of the P-P or R-R interval was noted. The circulation time observed varied from 1.6 to 16 seconds.

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Table I - Summary of Data

Sex	Age (yrs.)	Dose (mg)	Circulation Time (secs.)	Asystole Duration (secs.)	Sinus Acceleration Onset after Injection (secs.)
M	70	40	7.4	1.8	21.0
F	20	30	16.0	P-P Prolonged	26.8
		30	5.2	P-P Prolonged	15.8
F	31	40	7.7	3.8	None
M	44	20	No Results	None	None
		40	No Results	None	None
		50	4.9	2.4	19.7
		30	7.2	P-P Prolonged	None
M	56	20	No Results	None	None
		30	2.8	P-P Prolonged	None
		30	2.2	P-P Prolonged	None
M	58	40	9.0	P-P Prolonged	None
		40	No Results	None	None
M	75	40	No Results	None	9.1
		50	7.8	3.6	None
F	69	40	7.0	P-P Prolonged	None
		40	4.4	P-P Prolonged	None
F	65	40	9.4	P-P Prolonged	None
		40	11.3	1.7	None
M	22	40	No Results	None	None
		40	6.6	P-P Prolonged	None
		40	No Results	None	None
M	17	40	4.8	1.4	20.3
		40	3.9	1.4	None
F	58	40	7.6	P-P Prolonged	None
F	56	40	4.0	1.2	None
M	42	40	4.1	2.7	10.4
F	65	40	6.2	1.4	None
F	17	30	4.3	1.0	13.5
		30	5.2	1.0	17.7
F	53	30	7.9	R-R Prolonged	None
		40	8.6	R-R Prolonged	None
		40	9.3	R-R Prolonged	None
F	34	40	5.3	P-P Prolonged	14.2
		40	3.7	P-P Prolonged	None
		40	3.6	P-P Prolonged	None
F	65	40	14.0	1.4	None
		40	10.6	1.4	None
M	72	40	No Results	None	None
		40	6.8	P-P Prolonged	None
M	36	40	2.8	P-P Prolonged	8.9
		40	2.3	P-P Prolonged	11.5
M	58	40	3.6	1.8	None
		40	3.0	1.3	None
		40	3.2	P-P Prolonged	None
		40	1.6	1.2	None
M	49	25	No Results	None	None
		40	9.0	P-P Prolonged	None
M	49	40	6.1	P-P Prolonged	None
M	60	40	8.4	P-P Prolonged	22.6
		40	9.9	1.2	23.2
F	31	10	No Results	None	10.0
		20	No Results	None	7.1
		30	10.2	P-P Prolonged	17.1
F	32	15	2.8	P-P Prolonged	7.6
M	68	20	No Results	None	None
		25	7.0	1.2	
M	60	20	6.4	1.4	None

TABLE 2

Dosage	Successful Tests	Number of Tests
10 mg.	0	1
15 mg.	1	1
20 mg.	1	5
25 mg.	1	2
30 mg.	9	9
40 mg.	32	38
50 mg.	2	2
Total	46	58

(on 29 cases)

In 15 of the 37 cases a distinct sinus acceleration was seen. This occurred after an average elapsed time of 16.7 seconds, the range being 7.6 seconds to 26.8 seconds. Twenty patients had a cough reaction. In 2 instances transient bigeminal rhythm was

**Discussion.** The results indicate that acetylcholine offers a clear end point for the objective determination of circulation time in man. The doses used caused varying degrees of sinus slowing or asystole. The minimal dose evoking such response varied in the different patients, but the average was 40 mg. Inasmuch as doses of more than 60 mg. were not administered, failure to obtain a circulation time measurement in some patients may have been due to inadequate doses. It is possible that if larger doses than 60 mg. had been employed, a positive result might have been obtained. This

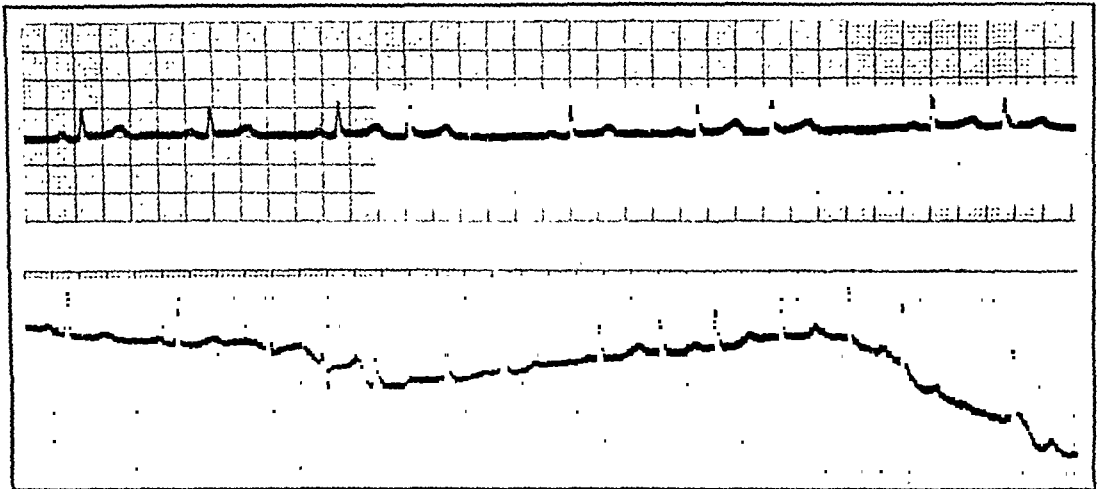


FIG. 1—ELECTROCARDIOGRAMS (VISO-CARDIETTE) LEAD 2.

Upper tracing shows the occurrence of bigeminal rhythm (nodal) 6.8 seconds after the administration of 40 mg. of acetylcholine.

Lower tracing shows the occurrence of auricular fibrillation beginning 16.0 seconds following the injection of 25 mg. of acetylcholine.

seen. Premature systoles occurred in 3 cases, one each of auricular, nodal and ventricular origin. In 2 patients auricular fibrillation developed 16.0 and 20.4 seconds respectively after the injection of acetylcholine.

Eight of the 37 patients showed no asystole or prolongation of P-P or R-R interval after a total of 23 injections of acetylcholine. However, 4 of these patients had a cough reaction, and of these 3 showed sinus acceleration after 9.6, 13.0 and 21.0 seconds. Two patients had auricular fibrillation initially and the response to acetylcholine was difficult to evaluate because of gross irregularity of the ventricles, but the circulation time was increased even though there was no congestive failure present.

is suggested by the appearance of a cough reaction and sinus acceleration in some of the negative cases.

The action of the drug on the heart on the basis of our animal experiments<sup>12</sup> appears to be a direct one whereby the acetylcholine passes via the coronary vessels to the sinus node and the A-V junction bringing about the effect discussed.

A correlation of the circulation time with other clinical and laboratory findings has shown that the normal circulation time varies between 1.2 to 6 sec-

onds. Circulation times between 6 and 7 seconds were considered to be borderline and over 7 seconds were found to be definitely abnormal.

Compared to other methods acetylcholine yields a distinctly shorter circulation time. The small volume and short duration of the injection reduced the range of variation seen with the sodium cyanide<sup>5</sup>, thiamine<sup>9</sup> and diodrast methods.

The exact cause of the cough is not clear, but it appears to be a vagal reflex arising from the stimulation of end organs in the bronchial tree. In dogs, the cough has apparently been eliminated by cutting of the vagi<sup>12</sup>. The sinus acceleration, which is a delayed phenomenon may be attributed to elaboration in the heart by acetylcholine of epinephrine-like substances. This is suggested by the experiments of McDowall<sup>6</sup> and Hoffman *et al.*<sup>2</sup> There was in our cases a significant drop in blood pressure in only 1 patient, a case of myocardial infarction. Apparently the depressor action of acetylcholine is a direct effect on the heart and blood vessels. This effect seems to be neutralized by its stimulation of the sympathetic nervous system. The premature beats seen in three cases may be due to a direct action of acetylcholine on the heart or to the liberation of epinephrine-like substances following the exhibition of acetylcholine. It is not due to a cholinergic coronary vasoconstriction. Previous animal experiments in this laboratory have shown that acetylcholine is a coronary dilator and that its effects on the coronary vessels may be abolished by atropine<sup>6,13</sup>. The only constrictor fibers to

the coronary artery are adrenergic<sup>3</sup>.

The only serious objection to the use of acetylcholine for the determination of circulation time in man is the induction of multiple premature systoles and auricular fibrillation. The latter was observed in 2 of our cases. Both patients had hypertension and coronary sclerosis and one also was markedly anemic. Auricular fibrillation has been produced experimentally by the administration of acetylcholine<sup>1,8,12</sup>. In human and animal experiments it has also been observed after the injection of acetyl- $\beta$ -methylcholine<sup>7,11</sup>. Smith and Wilson<sup>11</sup> attributed auricular fibrillation to the combination of anoxia and vagus stimulation and our own observations show that anoxia and vagus stimulation are important causative factors in producing auricular fibrillation<sup>10</sup>. The margin of safety may be very small. In one case, 20 mg. of acetylcholine had no effect on the patient whereas 25 mg. produced asystole followed by auricular fibrillation. In both cases in our series in which auricular fibrillation occurred, the mechanism was broken and sinus rhythm re-established by the administration of oral quinidine. Atropine injections and oxygen inhalation did not abolish the arrhythmia.

**Conclusions.** We must conclude that while acetylcholine may be used for simple, accurate and objective measurements of circulation time in man, it can not be regarded as an innocuous procedure for the patient.

We are indebted to the medical staff of Michael Reese Hospital for permission to carry out these studies on their patients. We are indebted to Dr. L. N. Katz for his advice in carrying out this study.

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# A METHOD FOR STUDYING THE EFFECT OF VARIOUS SUBSTANCES UPON RED CELL MATURATION IN-VITRO\*. †

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SINCE the therapeutic value of liver in the treatment of pernicious anemia was reported by Minot and Murphy<sup>12</sup>, there have been many attempts to ascertain the cause of this disease and to explain the mechanism by which remission is induced as a result of liver therapy. As liver fractionation procedures have progressed from the early separations of Cohn and his coworkers<sup>2</sup> to the highly purified preparations of Karrer and his coworkers<sup>9</sup>, and the multiple factors of Jacobson and Subbarow<sup>8</sup>, there have been repeated efforts to produce a syndrome in an experimental animal identical with that found in the human pernicious anemia patient in order to test the products obtained during the course of such fractionation processes.

Nutritional anemias of various types; anemias due to treatment of the experimental animal with some toxic material such as phenylhydrazine, benzene, saponin, or lead salts; and the anemia resulting from splenectomy have all been tried in an attempt to find an experimental assay method by which liver extracts could be standardized for their antipernicious anemia potency. None of these attempts have yielded a specific test method for anti-anemic substances. In addition, efforts have been made to accelerate the normal replacement of the fetal type of erythrocytes by their adult types and utilize this as an assay method. Studies made upon rat<sup>10a</sup>, opossum<sup>10b</sup>, and

chick embryos<sup>6</sup> indicate that this approach to the assay problem is not fruitful.

The clinical treatment of pernicious anemia patients with synthetic *L. casei* factor (folic acid or pteroylglutamic acid) has been reported by Spies and his coworkers<sup>16</sup>. This material also has been used in the study resulting from feeding monkeys highly purified diets<sup>3</sup>. Because of the similarity of the clinical response obtained from synthetic *L. casei* factor and antipernicious anemia liver extracts these reports should serve to caution investigators seeking an assay method which will respond specifically to liver extracts‡. It remains desirable that a specific method of assay for liver preparations be developed both to facilitate further fractionation of these extracts and also to secure information concerning the mode of action of these materials in producing new red blood cells.

Two claims<sup>14,15</sup> of a satisfactory assay method for the antipernicious anemia principle utilizing bone marrow segments clotted in serum have been investigated by others and found to be non-specific<sup>5,18</sup>. Recently a modification of this method has been reported<sup>1</sup> as useful for testing the antipernicious anemia property of liver extracts. However, in this report it is stated that folic acid gives a migration of cells from the bone marrow transplants similar to that obtained with liver extracts.

Osgood and Brownlee<sup>13</sup> report that

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† I wish to acknowledge the grant from The Armour Laboratories, of Chicago, Illinois, which made this work possible.

‡ We have observed, for example, that both synthetic *L. casei* factor and potent liver fractions stimulate reticulocytosis in splenectomized rats kept upon an adequate, highly purified diet. This type of anemia, therefore, cannot be utilized for specifically testing the anti-anemia potency of liver extracts.

if a bone marrow cell culture technique is used, sera from patients with pernicious anemia in relapse do not support bone marrow cell growth while sera from normal individuals do. These workers also report that liver extract stimulated erythropoiesis in the former case.

The obvious conclusion from the work referred to above is that of all of the methods which might appear suitable for an assay procedure to test specifically the antipernicious anemia potency of liver extracts, a study of some of the factors involved in red cell maturation and formation in the bone marrow itself is most likely to be successful. It would seem possible that if different erythropoietic substances stimulate different phases of red cell production and maturation this fact would become apparent during the course of such a study. For this reason a study of some of the factors involved in red cell maturation within the bone marrow was undertaken in this laboratory late in 1945. As a result of this work a technique has been developed for measuring some substance (or substances) involved in red cell maturation which is present in potent antipernicious anemia liver extracts, human and rat serum, and which is not the synthetic *L. casei* factor nor its conjugated form (vitamin B<sub>12</sub> conjugate).

The use of *invitro* tissue survival technique offers an advantage over *invivo* experiments in that it removes the process under consideration from the factors within the body which may influence it. In the case of bone marrow cells simply removing them from the body eliminates the influence of the gastro-intestinal tract, the liver, the various hormones, and the variations in

oxygen tension all of which markedly influence erythropoiesis. By centrifuging the marrow cells it is possible to remove the majority of the mature red cells and thereby concentrate the immature forms for study. The conditions outlined here have been developed as a result of a number of experiments during which the best medium for the suspension of the cells, the length of the incubation period, the proper method for concentrating the immature cells, and the stage of maturation most readily measured have all been determined.

Rats were chosen as a source of the bone marrow cells because of their relative uniformity, low cost, and because of the fact that their bone marrow cells appear to respond to human serum as well as to their own. Bone marrow from male animals appears to give a more uniform response than that taken from females. The size of the animal is important, those weighing from 140 to 180 grams giving the best results.

**Method.** The animal is killed by a blow on the back of the head and the bone marrow cells from both femurs are removed immediately by cutting the bone near the proximal end and aspirating the cells with the aid of a 1 ml. syringe fitted with a 20 gauge needle. The presence of a small amount of suspension fluid\* in the syringe aids in washing the cells from the bone cavity. Approximately 0.5 ml. of fluid is used in 0.1 ml. portions to wash out each bone. The pooled samples are collected in a 30 mm. piece of pyrex glass tubing having an outside diameter of 8 mm. and which has been drawn to a capillary approximately 1 mm. in bore and 25 mm. long and sealed at the end to form a centrifuge tube.† The large end of this centrifuge tube is fitted with a sterile rubber ampoule closure. The tube and its contents is spun in an International Micro Centrifuge for 30 minutes (approximately 1800 r.p.m.). The fluid and any floating lipid material is care-

\* The medium used throughout is a modified glucose-free Tyrode solution made up as follows: 8.0 gm. NaCl, 0.4 gm. KCl, 0.2 gm. CaCl<sub>2</sub>·2H<sub>2</sub>O, 0.1 gm. MgCl<sub>2</sub>, and 5.0 ml. Normal H<sub>3</sub>PO<sub>4</sub> (Standardized by titration with standard NaOH to pH 4.3 and multiplying by three), are added to 50.0 ml. of redistilled water. This is the stock salt solution. It is placed in small test tubes and sterilized by placing them in a water bath at 100° C. for 30 minutes. For the final medium 12.0 ml. of this solution and 0.2 ml. of an approximately 5 Normal Na<sub>2</sub>CO<sub>3</sub> solution (53.0 gm. of C. P. Na<sub>2</sub>CO<sub>3</sub> dissolved in 200 ml. of redistilled water and sterilized as above) are added to 240 ml. of sterile glass-distilled water. This final medium is prepared daily. The pH of the medium is 7.4.

† All glassware, including syringes, is dry sterilized at 160° C. overnight.



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fully removed by suction through a sterile glass tube and the mature red blood cells which form a layer at the bottom of the capillary tube are removed by marking the capillary just above this layer with a diamond pencil and breaking it at this point. The mature red cell layer is discarded. The cells remaining in the tube are forced into a second centrifuge tube of similar design with approximately 1 ml. of medium. After suspending the cells by gentle agitation, this second tube is spun for 15 minutes in the centrifuge and again the lower mature red cell layer is discarded after removing the fluid layer. The cells are suspended in 0.8 ml. of medium and after thorough mixing they are ready to be placed in the incubation tubes. Additional centrifugations appear to diminish the amount of maturation obtained from the preparation.

A satisfactory procedure for preparing the dilutions of the material to be tested is as follows: 0.5 to 1 mg. of the material is as tested is weighed on the microbalance in a small platinum boat. The material in the boat is dissolved in a sufficient volume (5 to 10 ml.) of the sterile glucose-free Tyrode solution to make a concentration of 100  $\mu$ g. per ml.\* This solution is then diluted to the desired concentration with glucose-free Tyrode solution in a series of small sterile test tubes using syringes to transfer the liquids from one tube to another. For a preliminary test of the potency of an unknown material it has been found desirable to dilute the 100  $\mu$ g per ml. stock solution to a series of solutions having final concentrations of 10.0, 0.1, 0.001, and 0.00001  $\mu$ g per ml.

Sterile tubes 40 mm. in length made of 8 mm. outside diameter Pyrex glass tubing sealed at one end are used for the incubation of the bone marrow cells. Rubber ampoule closures, which have been sterilized by boiling for 30 minutes, are used to plug the tubes during incubation.

The solution to be tested is placed in the incubation tube by means of a sterile 90 to 100  $\mu$ g. Lang-Levy micropipette.<sup>11</sup> If serum is being tested 45 to 50  $\mu$ l of serum and an equal volume of glucose-free Tyrode solution are added to the tube. To each tube is then added, by means of another micropipette, 90-100  $\mu$ l. of the bone marrow cell suspension mentioned above. After gentle mixing the

tubes are incubated in a 38° C. water bath for a period of 3 hours.

At the end of the incubation period the tubes are placed on ice in order to prevent further maturation while they are being counted. The counting of the mature reticulocytes<sup>§</sup> is performed by gently, but thoroughly, agitating the tube of cells until a uniform suspension is secured and then transferring a drop of this suspension to a hemocytometer chamber. In place of the heavy glass coverslip ordinarily used with the hemocytometer chamber a thin coverslip is used. This coverslip is previously stained with Brilliant Cresyl Blue by evaporating a drop of a saturated methyl alcoholic solution of the dye upon its surface. The dyed surface is placed face downward upon the chamber and mounted there with strips of "scotch" tape in order to prevent the cover slip from shifting during the manipulation while the count is being made under the oil immersion lens. The use of a thin coverslip permits careful observation of the cells with the aid of the oil immersion objective of the microscope. A minimum of 1,000 cells is counted for each tube<sup>†</sup> and the number of mature reticulocytes among these 1,000 cells is determined. The mature red cells are disregarded in counting the nucleated cells. The use of the hemocytometer chamber for counting cells in suspension has the advantage that the sides of the chamber support the weight of the coverslip and at the same time the ruling divides the field observed under the microscope so that an accurate count is secured.

Because of the length of time consumed by the cell counting process, only 7 tubes are incubated in any one experiment. However, 2 experiments may be run in a single day by delaying the second series until the first is incubating. A typical experiment includes 2 control tubes containing only glucose-free Tyrode solution in addition to the cell suspension, 4 different dilutions of substance being tested, and one tube containing 0.01  $\mu$ g per ml. of a liver standard preparation.<sup>••</sup> The inclusion of a standard liver preparation in each experiment permits one to calculate all of the results secured on a basis equivalent to a response obtained from a definite quantity of a single potent material. The data obtained from one sample of bone marrow, therefore, can be compared

\* It has been found that this solution need not be sterilized.  
<sup>§</sup> A reticulocyte is regarded as "mature" when only the barest trace of fine reticulum is present.  
<sup>†</sup> It has been found that this number of cells is adequate. Very good agreement has been obtained from quadruplicate counts of 1000 cells from the same sample.

•• The liver extract (Lot 11285A) used for the standard in this work was generously supplied by Dr. F. C. Koch of The Armour Laboratories. This material is the dry powder from which 15 U. S. P. unit liver extract is prepared and 17 mg. is equivalent to 1 U. S. P. unit.

directly with those from another. For purposes of such a comparison all results have been arbitrarily recorded in terms of the reciprocal of the amount of the unknown substance required to produce the same result as is obtained from 0.01  $\mu$ g. per ml. (or one of our units) of the liver standard. For example: If 0.001  $\mu$ g. per ml. of an unknown gives the same number of mature reticulocytes per 1000 nucleated cells as is produced by 0.01  $\mu$ g. per ml. of liver standard, the unknown would be recorded as having an activity of 10 units per microgram. This value indicates that the unknown is 10 times as active per unit weight as is the liver standard.

**Results.** The method outlined above has been used to study the erythrocyte maturation factors present in liver preparations and to determine whether there is a similarity between liver extracts, synthetic *L. casei* factor, and the substance affecting red cell maturation found in normal serum. Table 1 shows the results obtained when various liver fractions are tested by this method. Data secured when serum is added to the medium are also presented in this table.

Because of the clinical response ob-

TABLE 1. — EFFECT OF VARIOUS SUBSTANCES UPON IN-VITRO BONE MARROW SUSPENSIONS.

Substance Added to Substrate	Concentration in Micrograms per Ml.	Number of Mature Reticulocytes per 1000 Nucleated Cells		Potency in Units†
		Average*	Range	
None	.....	6 (135)	4-8	.....
Commercial Liver Extract				
15 Units per Ml.				
Lot No. E28403	.01	14 (2)	14-14	1.0
Lot No. D67503	.01	13 (4)	12-14	1.0
4 USP Units per Ml.				
Lot No. 10237	.24	14 (2)	13-14	.2
Lot No. 10238	.24	12 (2)	12-12	.2
Liver Fraction No. 101 §	1.0	8 (2)	8-8	.01
	.1	8 (2)	8-8	
Synthetic <i>L. casei</i> Factor	4.9	8 (2)	8-8	.002
Vitamin B <sub>6</sub> Conjugate	1.0	8 (2)	7-9	.01
Liver Standard	.1	12 (6)	9-20	
Lot No. 11285A	.01	12 (57)	9-18	1.0
	.001	13 (1)	13	
	.0001	10 (2)	7-14	
	.00001	6 (2)	6-6	
Normal Rat Serum	See Text	13-(20)	9-34	
Normal Human Serum	See Text	15-(4)	9-24	
Normal Human Serum plus Liver Standard	.005	20 (1)	20	
Normal Human Serum plus <i>L. casei</i> Factor	.005	15 (2)	15-15	

\* Numbers in parentheses give the number of individual experiments.

† The definition of the unit is given in the text.

§ This liver fraction was prepared in this laboratory from an active liver concentrate. When tested upon a pernicious anemia patient in relapse it was found to be inactive at a level of 17 mg. per day administered parenterally. This weight of material was derived from 240 gm. of fresh liver.

TABLE 2. — EFFECT OF THE B VITAMINS UPON IN-VITRO BONE MARROW SUSPENSIONS.

Substance Added to Medium	Concentration in Micrograms per Ml.	Number of Reticulocytes Per 1000 Nucleated Cells	
		Average*	Range
None	.....	7 (20)	3-8
Synthetic <i>L. casei</i> Factor†	4.9	8 (2)	8-8
	.05	8 (4)	6-9
	.0005	8 (2)	5-10
	.00005	7 (2)	7-7
Vitamin B <sub>6</sub> Conjugate†	1.0	8 (2)	7-9
	.1	7 (2)	7-7
	.01	6 (4)	5-8
	.001	6 (2)	6-6
Vitamin B-Complex Mixture§	2100.	4 (2)	4-4
	20.	5 (2)	4-6
	.2	5 (2)	4-6
	.002	6 (2)	6-6

\* Numbers in parentheses indicate the number of separate experiments.

† Courtesy of the Lederle Laboratories, Pearl River, New York.

‡ Courtesy of Dr. J. J. Pflieger, of Parke, Davis and Company, Detroit, Michigan.

§ Made up by dissolving 17.5 mg. of synthetic *L. casei* factor, 350 mc. p-aminobenzoic acid, 350 mg. thiamin chloride, 700 mg. riboflavin, 350 mg. pyridoxine hydrochloride, 700 mg. calcium pantothenate, 3,500 mg. nicotinic acid, 14,980 mg. choline chloride, and 250 micrograms of biotin in 100 ml. of water. The total solids of this mixture is approximately 209 mg. per ml.

tained with synthetic *L. casei* factor, this substance and its conjugate form were also studied. Table 2 records the data obtained together with that of an experiment in which a Vitamin B-Complex mixture was tried.

Various protein and carbohydrate substances and their derivatives have likewise been tested for maturation potency by this method. Table 3 shows the results obtained from these trials.

It will be noted that glutathione, l-tyrosine, and Bacto-yeast extract appear to have some red cell maturing effect. The effect of tyrosine is in accord with the report of SubbaRow<sup>8</sup> that tyrosine is one of the accessory factors in erythropoietic liver extracts and also the

poietic substance in addition to the vitamin B<sub>6</sub> conjugate which is itself inactive when this test method is used.

From the data recorded in the above tables it is apparent that the *in vitro* cell maturation technique described here appears to have some specificity for liver extracts. Further investigation will be required in order to prove whether or not this technique is specific for the antipernicious anemia substance. However, some factor (or factors) involved in red cell maturation is responsible for the observed maturation. This factor appears not to be the synthetic *L. casei* factor nor is it vitamin B<sub>6</sub> conjugate.

In a previous report<sup>4</sup> we have presented evidence to indicate that the

TABLE 3.\* — EFFECT OF NON-ERYTHROPOETIC SUBSTANCES UPON IN-VITRO BONE MARROW SUSPENSIONS.

Substance Added to Medium	Concentration in Micrograms per Ml.	Number of Mature Reticulocytes per 1000 Nucleated Cells
None	.....	6
<i>Amino Acids</i>		
d1-alanine	100.	7
1(-) tryptophane	100.	6
1(-) tyrosine	10.	12
Casein hydrolysate†	1000.	6
Glutathione	.001	10
<i>Proteins</i>		
Recrystallized Egg Albumin	100.	6
Gelatin	1000.	6
Crystalline Human Serum Albumin	100.	6
Bacto-yeast Extract	.1	11
<i>Carbohydrates</i>		
Glucose	100.	6
Sodium fructose 1,6 diphosphate	1000.	6
Lithium pyruvate	10.	6
Liver Extract Standard	.01	12

\* All values recorded in this table, with the exception of the liver standard, are the highest concentration tested. In each case a number of lower concentrations were tried and all of these gave the control value of approximately 6 reticulocytes per 1000 nucleated cells.

† The product prepared by General Biochemicals, Inc., was used.

report of Jacobsen and Plum<sup>7</sup> concerning the tyrosine requirement of the pernicious anemia patient to insure proper response to liver therapy. The slight effect of the yeast extract may be correlated with the report<sup>17</sup> of the use of large amounts of yeast to induce remission in pernicious anemia patients. The fact that yeast extract shows some maturation potency by the test method described here may indicate that there is present in yeast some erythro-

poietic substance in addition to the vitamin B<sub>6</sub> conjugate which is itself inactive when this test method is used. This substance is present in normal human and rat serum. Although the report was based upon findings in one case of pernicious anemia, it is believed to be of significance as a clue to the differences in the mechanism by which synthetic *L. casei* factor and the liver antianemia substance act in producing red cell maturation in the bone marrow.

**Summary.** An *invitro* cell survival technique is described for measuring the red cell maturing ability of liver extracts.

Data are given to indicate that the maturation is stimulated by antianemia liver preparations and is not observed when a number of other materials, including an inactive liver extract, is used.

Synthetic *L. casei* factor or its vitamin B<sub>6</sub> conjugate form, does not affect the maturation process studied by this method.

Normal human and rat serum exhibit the presence of the maturation factor required by this technique.

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# OBSERVATIONS CONCERNING THE EFFECTS OF BLOOD UPON THE ACTION OF A DIGITALIS GLYCOSIDE.\*

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IN a previous study,<sup>2</sup> it was found possible, by means of the embryonic duck heart preparation to detect as little as 0.05 micrograms of a digitalis glycoside (Lanatoside C) per cc. of Tyrode's solution. The extreme sensitivity of this preparation to glycoside in Tyrode's solution suggested the possibility that perhaps minute amounts of digitalis glycoside in blood also might be detected. In order to standardize this type of detection however, it was thought necessary to determine separately the effects of (1) blood cells, and (2) serum of whole blood. The results of such studies are reported herein.

**Results. A. THE EFFECT OF HUMAN BLOOD CELLS UPON DIGITALIS GLYCOSIDE.** Samples (1 cc.) of oxalated, fresh human blood from several subjects were centrifuged. The supernatant plasma was removed and was replaced by an equal amount of Tyrode's solution and the entire sample recentrifuged. This procedure was repeated 5 times in order that samples consisting of only blood cells in Tyrode's solution be obtained. Different amounts of Lanatoside C. were added to these final mixtures of Tyrode's and cells so that samples containing 0.2, 0.5 and 1.0 microgram

of glycoside per cc. were obtained. The latter were then shaken, allowed to stand for 15 minutes, and centrifuged once more. The supernatant fluid obtained was tested on the embryonic duck heart as described previously<sup>2</sup> except that the temperature of the fluid bathing the hearts was maintained at 35° C. If blood cells adsorbed or otherwise inactivated the glycoside, then this final supernatant Tyrode's solution might be expected to exhibit less "digitalis like" activity than control samples of Tyrode's solution to which the same amount of glycoside had been added.

Our studies (See Table 1) indicated that 1 cc. samples of Tyrode's solution containing 1.0 or 0.5 micrograms of glycoside were little if at all affected by contact with a quantity of blood cells equivalent to that in 1 cc. of whole blood. Thus, A-V block occurred in the duck hearts in 9 and 10 minutes respectively in supernatant fluid samples obtained from Tyrode's-cell mixtures to which had been added 1.0 and 0.5 micrograms of glycoside per cc. respectively. Compared to the time of occurrence of A-V block (7 and 10 minutes) in control Tyrode's solutions alone containing 1.0 and 0.5 micrograms of glycoside per cc. respectively, it was questionable whether a signifi-

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cant difference existed. However, supernatant fluid obtained from mixtures originally containing 0.2 micrograms of glycoside per cc. produced A-V block after an average period of 25 minutes which was significantly longer than the time (18 minutes) required for A-V block in hearts exposed to pure Tyrode's solution containing 0.2 micrograms of glycoside per cc. It would appear then that blood cells were capable of adsorbing or inactivating a fraction (albeit minute) of the digitalis glycoside.

B. THE EFFECT OF SERUM UPON DIGITALIS GLYCOSIDE. (1) *The Effect of Rat Serum.* To 1 cc. samples of fresh rat serum, quantities of glycoside varying from 0.01 to 2.0

The behavior of duck hearts in rat serum containing glycoside was unlike that of similar hearts in Tyrode's-glycoside solution in that the appearance of a "digitalis effect" was prolonged at all concentrations of glycoside employed. When only 0.01, 0.05 or 0.1 microgram of glycoside per cc. was present, the hearts beat exactly as did those in control serum. When 0.2 micrograms of glycoside per cc. was present, 20 hearts beat for an average period of 43 minutes before exhibiting a "digitalis effect" which was of course much longer than the time (18 minutes) taken by hearts exposed to the same amount of glycoside in Tyrode's solution. As Table 1 and Figure 1 indicate, this retardation in the occurrence of

TABLE 1. THE EFFECT OF (1) BLOOD CELLS, (2) PLASMA PROTEIN AND (3) ALBUMIN UPON THE ACTION OF DIGITALIS GLYCOSIDE

CONC. OF GLYCOSIDE. μg./cc.	TIME OF OCCURRENCE OF "DIGITALIS EFFECT" (Minutes)			
	TYRODE'S	TYRODE'S & BLOOD CELLS	TYRODE'S & PLASMA PROTEIN	TYRODE'S & ALBUMIN
0.2	18 (25)	25 (9)	23 (24)	30 (12)
0.5	10 (17)	10 (5)	13 (20)	13 (19)
1.0	7 (14)	9 (11)	8 (13)	8 (13)

(Numbers in parentheses indicate number of separate duck hearts observed.)

micrograms were added. These samples as well as ones of pure serum alone were then stored in the refrigerator for 24 hours. At the end of this time, the samples were warmed to 35° C., embryonic hearts were placed in them and the time taken for the "digitalis effect" was recorded. It should be mentioned that in serum it was found that not only might the glycoside produce A-V block and missing beats but also it might markedly slow the rate of beating. Since the embryonic heart invariably was found at 35° C. to beat regularly in pure rat serum at a rate of 75 per minute for over 80 minutes, a heart in serum plus glycoside, which beat at a rate below 70 per minute was judged as indicating a "digitalis effect."

"digitalis effect" occurred at all dilutions although the divergency became less when concentrations of 1 microgram per cc. were employed.

(2) *The Effect of Human Serum.* Samples of human serum, containing various quantities of glycoside were prepared exactly as described for rat serum samples. As in rat serum, hearts in human serum also sometimes indicated the "digitalis effect" by marked slowing of beating. This type of phenomenon rarely occurred until less than 0.5 micrograms of glycoside per cc. was employed.

As Table 1 and Figure 1 demonstrate, the times of occurrence of the "digitalis effect" in hearts exposed to various concentrations of glycoside in human serum were almost identical

with those of hearts in rat serum and glycoside except that hearts in human serum were found to exhibit a "digitalis effect" when in contact with 0.1 micrograms of glycoside per cc. Therefore, human serum, similar to rat serum, differed from Tyrode's solution in that glycoside when dissolved in human serum was not able to effect a "digitalis effect" as rapidly as in Tyrode's solution.

The protein solution then was diluted with Tyrode's solution until a solution containing 6 gm. of plasma protein per 100 cc. was obtained. The pH of this solution was 7.2. Samples of this solution, containing 0.2, 0.5 and 1.0 microgram of glycoside per cc. then were tested on the embryonic duck hearts.

As Table 1 and Figure 1 demonstrate, plasma protein in Tyrode's so-

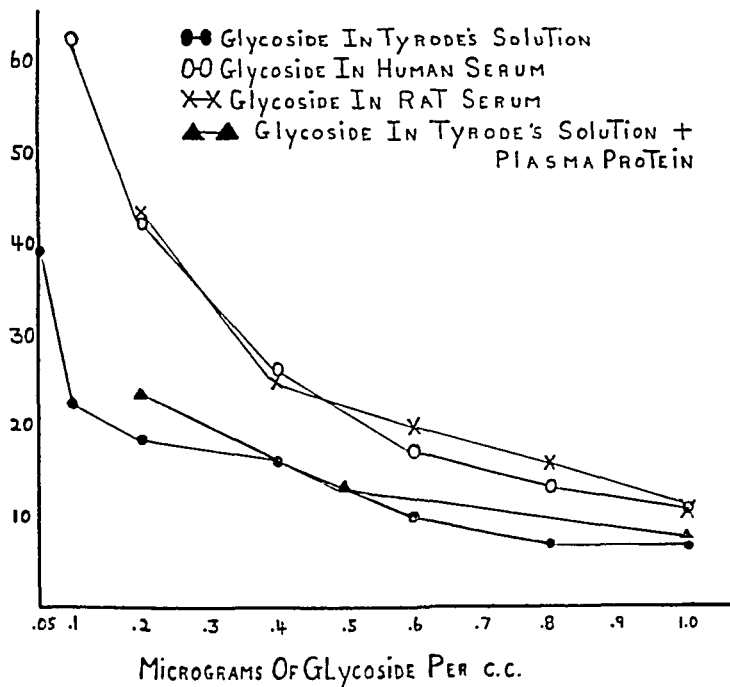


Fig. 1.—Time of occurrence of "Digitalis Effect."

C. THE EFFECT OF PLASMA PROTEINS UPON DIGITALIS GLYCOSIDE. In view of the fact that both rat and human serum were found to retard the actions of glycoside, it was thought that this retardation might be due to the protein content of the serum. Accordingly, the effects of both albumin and globulin together, as well as albumin alone, were tested. Samples of lyophilized human plasma were dialyzed against pure Tyrode's solution at 70° C. for approximately 48 hours.

lution did not appear to inhibit significantly the action of either 1.0 or 0.5 microgram of glycoside. Thus, 13 hearts exhibited A-V block, 8 minutes after contact with 1.0 microgram of glycoside per cc. and 20 hearts showed A-V block, 13 minutes after contact with 0.5 microgram of glycoside per cc. However, 24 hearts exposed to 0.2 microgram of glycoside per cc. did not exhibit A-V block until after an average period of 23 minutes. When this last is compared to the time taken for

the 25 hearts in the control Tyrode's solution, containing 0.2 microgram of glycoside per cc. to exhibit A-V block (See Table 1), it is probable that the plasma proteins did inhibit the action of this small amount of glycoside.

Similar results were obtained with the Tyrode's albumin solution, containing glycoside (See Table 1) in that little or no effect by the protein was observed on 1.0 or 0.5 microgram of glycoside per cc. Again, however, when there was only 0.2 microgram of glycoside in each cc. of the solution, A-V block did not occur in 12 hearts until an average period of 30 minutes had elapsed. Compared to the control value of 18 minutes, this delay in occurrence of A-V block must be regarded as significant.

**Discussion.** The above studies indicated that both rat and human serum markedly retarded the action of the particular glycoside (Lanatoside C) employed in the experiments. This comparative retardation, however, was not marked at a moderate concentration of glycoside (1.0 microgram per cc.) but only at low concentrations (below 1.0 microgram per cc.). This last fact may well explain the failure of our findings to agree with those of Suter.<sup>5</sup> This last investigator could not detect any serum retardation of the actions of Lanatoside C, but the amount of glycoside tested (2.0 microgram per cc.) might have been too excessive to reveal the inhibiting effect of serum.

If human serum, however, was found to delay the action of the glycoside, it was found that this retardation could not have been due to its protein content alone. For when the lyophilized protein content of human plasma was dissolved in Tyrode's solution, its inhibition of glycoside was slight. Similar results were obtained when pure dried albumin was dissolved in Tyrode's solution containing glycoside.

Previously it was observed<sup>3</sup> that when the calcium content of Tyrode's solution was reduced to 5 mg. per 100 cc. the action of Lanatoside C was inhibited markedly. This inhibition was later found<sup>4</sup> to be due to the action of potassium in Tyrode's solution which previously had been held in check by the amount of calcium usually present in Tyrode's solution. In view of this previous finding and the fact that serum probably contains only about 5 mg. of calcium per 100 cc. in an ionized state,<sup>1</sup> it is possible that the retardation of glycoside in serum was not primarily due to the action of the latter upon the drug but rather to the inability of the embryonic heart (in a medium low in ionized calcium) to respond quickly to the glycoside.

It was of particular interest to us, however, that as little as 0.1 microgram of glycoside in 1 cc. of human serum could be detected by means of the embryonic duck heart preparation. Perhaps even more important, was the finding that the time of occurrence of a "digitalis effect" in the duck heart depended upon the concentration of glycoside in serum. This last finding allows the possibility of making quantitative assays of the content of glycoside in any given serum sample suspected of containing it.

**Conclusions.** (1) The response of the embryonic duck heart to a digitalis glycoside (Lanatoside C) was found to be slightly retarded by blood cells, plasma protein and pure albumin.

(2) Rat and human blood serum, however, were found to inhibit markedly the effect of the glycoside upon the duck hearts. This effect was thought to be due in part to the relatively low concentration of ionized calcium in the 2 sera.

(3) Detection and quantitative assay digitalis glycoside in fractions of less than a microgram per cc. of human serum were studied.



TABLE 2. THE EFFECT OF HUMAN AND RAT SERUM UPON THE ACTION OF DIGITALIS GLYCOSIDE

CONC. OF GLYCOSIDE $\mu\text{g./cc.}$	TIME OF OCCURRENCE OF "DIGITALIS EFFECT" (Minutes)					
	TYRODE'S		HUMAN SERUM		RAT SERUM	
	Ar.	Range	Ar.	Range	Ar.	Range
0.01	—	—	—	—	—	—
0.05	39(14)	35-45	—	—	—	—
0.10	22(19)	16-30	62(32)	59-70	—	—
0.20	18(38)	15-19	42(39)	34-50	43(20)	36-51
0.40	16(20)	13-20	26(22)	19-32	25(22)	19-31
0.60	10(16)	9-11	17(18)	10-23	20(23)	16-25
0.80	7(20)	5-11	13(22)	9-20	16(20)	14-18
1.00	7(30)	5-9	11(15)	7-12	11(20)	9-12

(Numbers in parentheses indicate number of separate duck hearts observed.)

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# CONGENITAL HEMOLYTIC ICTERUS IN THE NEGRO

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CONGENITAL hemolytic icterus is rare in the Negro. Several descriptions of this disease in negroes have recently appeared. Wintrobe<sup>13</sup> has observed the disorder in a mulatto. Smith and Drake<sup>8</sup> reported hemolytic icterus in a 22 year old negro male but it was not established as a congenital type. Stragnell and Smith<sup>9</sup> described the syndrome in a 21 year old negro male and 2 sisters. These same authors, upon reviewing the clinical records of two decades at the Presbyterian Hospital, New York City, found 1 case of spherocytic acholuric hemolytic jaundice in a mulatto. Scherer and Cecil<sup>7</sup> have reported the disease in a 14 year old negress and erythrocyte microcytosis in a maternal uncle and the maternal grandfather. Merskey and Baskind<sup>5</sup> reported a condition occurring in a native of the Northern Transvaal characterized by icterus, spherocytosis, increased osmotic fragility of the red cells, splenomegaly and leg scars. Goodman and Cates<sup>3</sup> presented the findings in a negro family in which 3 sisters were found to have congenital hemolytic icterus.

This case is presented as a well-established example of congenital hemolytic icterus in the Negro complicated by gall bladder disease and treated by splenectomy. Included in the report are chemical and hematological data before and after splenectomy, and a discussion of the pathophysiological features of the disease as manifested by this patient. An additional feature of

interest: this patient is a maternal aunt of the case reported by Scherer and Cecil<sup>7</sup>.

**HISTORY:** E. M., a 26 year old negro housewife was admitted to this hospital, on January 17, 1947, with a history of mid-epigastric pain for 3 months. The pain was sharp, recurrent, non-radiating, occurring after meals and associated with eructations, nausea and vomiting. There was intolerance to fatty foods. The pain was relieved by vomiting and occasionally by soda. Six days before admission the pain became very severe and cramping and vomiting more frequent. Four days before admission she noted jaundice of the sclerae, dark urine, and light brown stools. The day before admission all pain subsided and the jaundice decreased. During the 3 months of abdominal pain her menses were more frequent and characterized by prolonged and excessive bleeding. There was a 10 pound weight loss.

One year previously, following a month of recurrent abdominal pain and a vaginal discharge, she was admitted to a hospital and treated with penicillin. For a 2½ year period ending 1 year before the present admission she was employed removing casings from storage batteries with an unknown solvent.

The patient's father, 3 brothers and 2 sisters are alive and well. Her mother died of diabetes and was known to have had gall bladder disease. One brother died of "poisoning". A sister had an episode of jaundice following the delivery of a normal child. This was attributed to a transfusion reaction. One sister died in childbirth. A daughter of this sister is known to have had an anemia "rare in colored people", and was treated by splenectomy with relief of the anemia.<sup>7</sup> A maternal half-sister had gall bladder disease.

**PHYSICAL EXAMINATION:** The patient was well developed and well nourished and did not appear acutely ill. Her temperature



to be lymph nodes which were filled with masses of erythrocytes, leucocytes, detached endothelial cells, and occasional large multinuclear cells. Phagocytic mononuclear cells were also present. Some of the latter were laden with hemosiderin granules but ingestion of intact red cells was not conspicuous. It was the impression of the pathologist that the "histological changes in the spleen (were) similar to those that have been described in congenital hemolytic icterus".

On March 12, 1947, Cholecystectomy was performed without complication.

**PATHOLOGICAL REPORT** (in summary): The gall bladder measured 5.5 cm. in length and was thick walled. The lumen

is rare in the Negro. This is an additional case of congenital hemolytic icterus in a Negro, a member of a family in which hemolytic icterus has already been reported. The cases of Stragnell and Smith,<sup>9</sup> Scherer and Cecil<sup>7</sup> and Goodman and Cates<sup>3</sup> appear to fulfill the clinical criteria of congenital hemolytic icterus but in the case presented by Smith and Drake<sup>8</sup> the rôle of sulfonamides as hemolytic agents must be considered. The question of malaria confuses the diagnosis in the case re-

TABLE 3—BLOOD CHEMICAL DATA

Date 1947	Icteric Index	Cholesterol MG %	Serum Protein GM %	Albumen Globulin	Alkaline Phosphatase Bodansky Units	Cephalin Flocculation	N.P.N. MG %	Uric Acid MG %
20 Jan.	25		6.2	3.8	9.4	Negative	28	
27 Jan.	15	95		2.4	3.6			
29 Jan.	20	114	5.4	3.0				
				2.4				
1 Feb.	14							
3 Feb.		130						1.5
17 Feb.	SPLENECTOMY							
28 Feb.	6	148	6.9					
12 Mar.	CHOLECYSTECTOMY							
24 Mar.		105		3.3			25	
28 Mar.	4	122	5.9	2.6	2.7	Weakly positive		

contained an oval 2 x 1½ x 1½ cm. black stone which, when cut, had a brownish core. On microscopic examination the gall bladder mucosal folds were flattened and ulcerated in a few areas. The wall was markedly thickened and lying just under the mucosa were polymorphonuclear leucocytes, monocytes and a few multi-nucleated macrophages. Some of the latter contained yellowish-brown pigment. The wall was edematous and the blood vessels engorged. There was much fibrosis in the muscularis and serosal layers. The gall stone was analyzed and found to contain mainly cholesterol, more biliverdin than bilirubin and small amounts of calcium, phosphorus and iron.

Hematological and chemical studies were repeated post-operatively and the results are presented in Tables 1, 2, and 3. The patient was discharged on March 30, 1947. She was seen in the clinic on April 11, 1947, and blood studies repeated. She appeared well at this time and offered no complaints. Further studies have been prevented by the patient moving to the South.

**Comment:** The literature indicates that congenital hemolytic icterus

ported by Merskey and Baskind<sup>5</sup>. The rarity of congenital hemolytic icterus in the Negro forces one to consider hybridism. Stragnell and Smith<sup>9</sup> and Goodman and Cates<sup>3</sup> found no evidence of racial admixture in their studies. Scherer and Cecil<sup>7</sup> obtained similar results with their case which has obvious application to the case here reported. A diagrammatic representation of the family in this case is shown in Fig. 1.

On admission, this patient exhibited resolving jaundice secondary to passage of a common duct stone. The changes in alkaline phosphatase supported this impression. The rôle of hemolysis in producing icterus could not be properly evaluated at this time. History of hemolytic episodes was singularly lacking and the anemia was minimal. The diagnosis of congenital hemolytic icterus was supported by the family history,

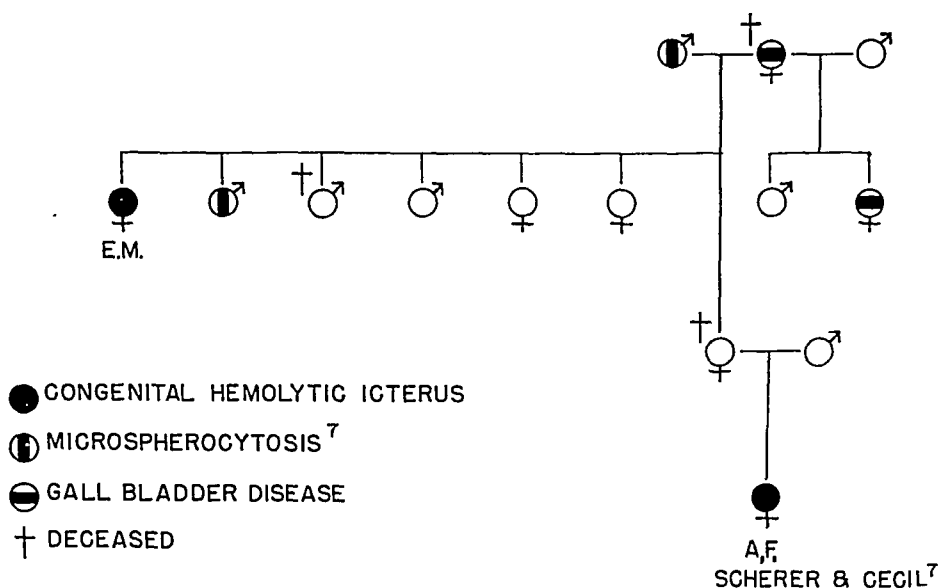
spherocytosis, splenomegaly, and increased erythrocyte fragility.

Spherocytosis is a characteristic finding in congenital hemolytic icterus<sup>4</sup>. There is no agreement about the effect of splenectomy on spherocytosis. Thompson<sup>10</sup> in a review of 45 cases reported that after splenectomy the spherical cells persist, and in one case were as high as 14% 16 years after operation. Vaughan<sup>12</sup> reported that although spherocytosis persists in rare instances after splenectomy, spherocytes are usually

well as the micro-spherocytosis. Quantitative cell diameter studies were not done in this case, but the spherocytes were significantly decreased in diameter. The concomitant fall in mean corpuscular volume and spherocyte percentage after splenectomy suggests a relationship between the two.

Reticulocytosis has been proposed to explain the increased mean corpuscular volume<sup>10</sup>. The reticulocytosis of 4.8% in this case fails to explain the increase in mean corpuscular volume. The

FIGURE 1 - REPRESENTATION OF FAMILY OF PATIENT E.M.



reduced and may disappear. In this patient there was a striking reduction in the number of spherocytes post-operatively, as indicated in Table 1.

An increase in mean corpuscular volume in congenital hemolytic icterus has been established in some cases<sup>10,12</sup>, and ascribed to increased cell thickness despite a decrease in mean cell diameter. Macrocytosis may occur in this disease and occasionally cause confusion with pernicious anemia<sup>13</sup>. Vaughan indicates that megalospherocytosis may occur as

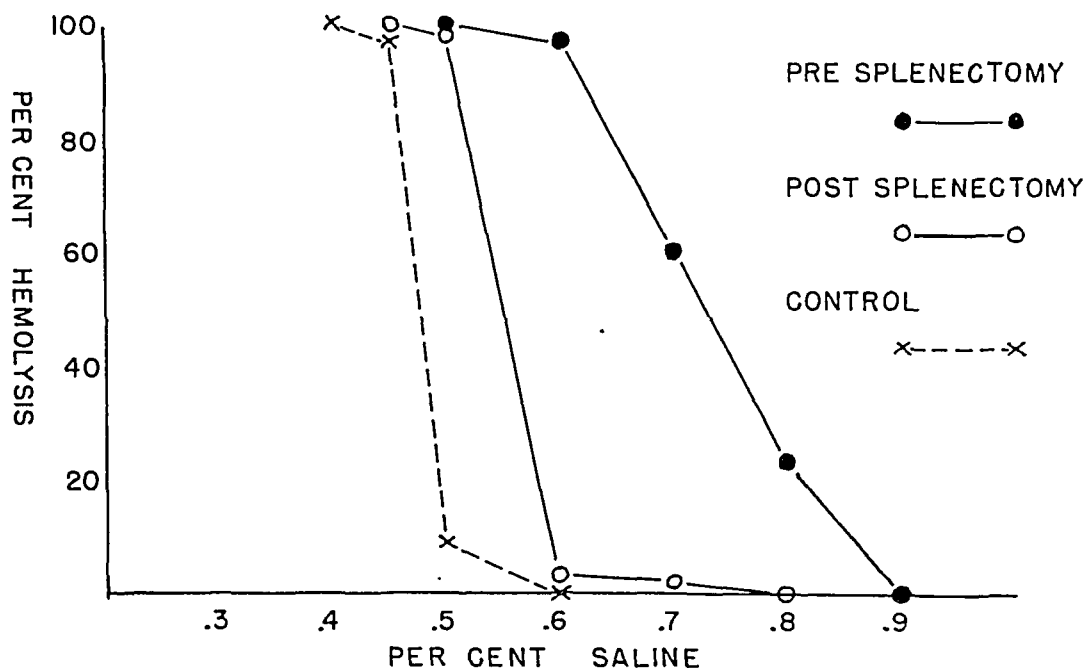
reticulocytosis in congenital hemolytic icterus is usually proportional to the degree of anemia reflecting the demand placed upon erythropoiesis. The relatively low reticulocyte count in this case is consistent with the degree of anemia. The reticulocyte count decreased as the erythrocyte and hemoglobin levels improved. The belief that reticulocytes are more resistant to hypotonic saline solutions than adult erythrocytes is not universally accepted<sup>13</sup>.

There is a growing impression concerning the effect of splenectomy that, although the hemolysis is inhibited, there is little change in erythrocyte fragility. This is not supported by the present study, nor by many earlier studies.<sup>6</sup> Animal experiments have revealed that removal of the normal spleen results in an increase in erythrocyte resistance to hypotonic salt solutions, hemolytic sera, and saponin<sup>6</sup>. Reported observations of erythrocyte fragility after splenectomy in congenital hemolytic icterus have varied. This

"diagonal" type of curve before splenectomy there was a change to the "tailed" type of curve with a shift of the hemolysis toward the normal. The hemolysis at 0.8% saline was decreased by 23%; at 0.7% saline it was decreased by 58%; at 0.6% saline it was decreased by 94%. These data indicate that splenectomy diminishes the erythrocyte fragility. In addition, there is a diminution in spherocytosis and in the mean corpuscular volume of the erythrocytes after splenectomy.

It is accepted generally that the

FIGURE 2 QUANTITATIVE HEMOLYSIS CURVES



variation may be evidenced as either a return to normal or an increase in the fragility.<sup>1,11,13</sup> Quantitative studies of the hemolysis have been performed in few instances. Such studies by Vaughan<sup>12</sup> and Dacie<sup>1</sup> have shown that the curves of hemolysis in congenital hemolytic icterus may be classified as "normal", "tailed", or "diagonal" in type. These workers have shown that after splenectomy there is a significant change in the form of the curves toward normal. Similar curves were obtained in this case (Fig. 2). From a

essential clinical features of congenital hemolytic icterus result from the breakdown in the spleen of the abnormally fragile cells. Recent studies by Emerson *et al*<sup>2</sup> indicate that the spleen in congenital hemolytic icterus serves as a site for "erythrocytostasis". As a result of this a rapid breakdown of the inherently defective erythrocytes occurs. In this and other reported cases<sup>1,12</sup> the decrease in hemolysis, following splenectomy, as determined quantitatively, is in accord with the view that the erythrocytes modified by stasis in

the spleen are no longer present.

It is concluded that the major abnormalities of the erythrocytes in congenital hemolytic icterus result from stasis in the spleen. Removal of the spleen brings about a change toward the normal. The primary inherent defect of the erythrocyte is unknown.

Summary: 1. Congenital hemolytic icterus in a 26 year old negress is reported.

2. Hematological and chemical data before and after splenectomy are recorded.

3. A discussion of the pathophysiological features of congenital hemolytic icterus as manifested by this patient is presented, with particular attention to the changes in spherocytosis, mean corpuscular volume of the erythrocytes, and the curves of erythrocyte fragility after splenectomy.

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# ANICTERIC HEPATITIS: A REPORT OF NINE SPORADIC CASES

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THE subject of anicteric hepatitis has been repeatedly mentioned in the numerous recent reports of infectious hepatitis<sup>2,8,12,13,14,19,20,23,35</sup>. The importance of its recognition and the significant clinical and laboratory criteria have been well emphasized. All of the cases described heretofore have, however, been highlighted by coincident epidemic hepatitis with jaundice. While the likelihood of recognizing anicteric hepatitis occurring sporadically has been noted,<sup>7</sup> there has been no such report in the literature. During the winter of 1946-1947, among the usual cases of acute infectious disease, we were fortunate in observing a number of cases which appeared to satisfy the criteria of anicteric hepatitis. This diagnosis was suspected because of the occurrence of marked upper abdominal complaints and laboratory evidence of liver damage following a non-specific febrile illness. During this same period 21 cases of sporadic icteric hepatitis were admitted to this hospital.

**Procedure.** Nine cases were studied, of which 4 were hospitalized and 5 were followed at home. Two were physicians, 1 a student nurse, 4 housewives and 2 laborers. Laboratory studies included: a hemogram, urinalysis, icterus index, urine urobilinogen, bromsulfalein excretion, cephalin flocculation and thymol turbidity tests. In 4 of the cases the Paul-Bunnell test for infectious mononucleosis was performed, and in 3 of the 4 the test was repeated after a 2-week interval. Urine urobilinogen was done by the method of Wallace and Diamond, in which the upper limit of normal is 1-20. The bromsulfalein

test was done by the method of Rosenthal and read spectrophotometrically. When done by this method, according to Mateer and his associates,<sup>22</sup> there should probably be no retention of dye at the end of 45 minutes. The absolute upper limit of normal is 5% retention at the end of this time. The cephalin flocculation test was done according to Neeff's modification of Hanger's original method.<sup>24</sup> The thymol turbidity test was done by MacLagen's method as adapted to the spectrophotometer by Shank and Hoagland.<sup>32</sup>

**Clinical Features.** The clinical picture (Table I) was that of a systemic disease with predominant abdominal localization. Onset in all of the cases save one was with fever. While only 1 patient had frank chills, chilly sensations were noted by 6 of the group. Frontal or orbital headache was present in an equal number. Mild sore throat was noted by 3 patients, but no other respiratory symptoms appeared in this group. Anorexia and epigastric fullness occurred in all. Soreness, a dull ache or intolerance to even the slightest pressure on the epigastrium, as well as actual right subcostal pain were noted in all cases. Flatulence, though rare during the febrile period, was always noted within a few days of onset. In one patient who reported no fever, the temperature was not taken for the first 2 weeks of his disease. Onset in this case was more insidious than in the remainder of the group. Pronounced fatigability, anorexia, backache, and epigastric fullness brought this patient to our attention.



Abnormal physical findings were sparse. Enlargement of only the cervical lymph nodes was found in 5 cases. Two patients showed a generalized lymph gland enlargement, and in 2 cases there were no abnormally palpable lymph nodes. Tenderness in the epigastrium or right upper quadrant of the abdomen was present. Frequently the equivalent of tenderness was a "queasy feeling" on right upper quadrant compression. The liver edge, palpable in all 9 patients, was found to

shift to the left noted in the first count, but in the second determination done two days later, return to normal had occurred. In 3 patients an eosinophil count of 5% was noted on the initial count. Urine urobilinogen was elevated in all cases. In 1 case the icterus index was elevated to 17 units. In another, with a normal icterus index, the blood bilirubin was slightly elevated. In the remaining 7 patients, there was no evidence of increased blood icterus. In all of the patients in whom the pro-

TABLE I - Clinical Features

Case	Age	Occu- pation	SYMPTOMS										SIGNS			
			Chilly Sensations	Fever	Malaise	Fatigue	Epigastric Fullness	Anorexia	Nausea	Vomiting	Headache	Sore Throat	Adenopathy	Hepatomegaly	Epigastric Tenderness	R.U.Q. Tenderness
J.R.	27	Physician	0	0	X	X	X	X	X	0	0	0	X	X	X	X
M.H.	21	Nurse	X	X	X	X	X	X	X	0	X	X	X	X	X	X
G.M.	23	Housewife	X	X	X	X	X	X	X	X	X	0	X	X	X	X
A.F.	29	Physician	X	X	X	X	X	X	0	0	X	X	X	X	0	X
J.B.	25	Housewife	X	X	X	X	X	X	0	0	X	0	X	X	X	X
I.H.	24	Housewife	X	X	X	X	X	X	X	0	X	X	X	X	X	X
W.B.	22	Laborer	X	X	X	X	X	X	0	0	X	0	X	X	X	0
J.E.	29	Social Wk.	0	X	X	X	X	X	0	0	0	0	0	X	X	X
R.B.	24	Laborer	X	X	X	X	X	X	X	0	X	0	0	X	X	X

extend from 2 to 4 centimeters below the right costal margin. In none of the patients was there any significant abnormalities in the nasopharynx or chest.

The white blood count in all patients was within normal limits or slightly depressed (Table 2). The highest count obtained was 9,500 per cm. and the lowest 4,200 per cm. The white cell distribution was also in the normal range in all cases except one. In this patient there was a marked

cedure was done, the bromsulfalein test showed evidence of impaired liver function varying from 80% to 6% retention. The cephalin flocculation test was positive in 5 cases. The thymol turbidity test was positive in 4 of the group but in the remaining 5 patients the values were between 3 and 4 units. It has been our experience, as well as of others<sup>24</sup>, that in normal subjects the result of the thymol test is less than 3 units, although MacLagen's original report<sup>32</sup> stated that turbidity

as high as 4 units was found in normal persons. The heterophile agglutinin reaction was negative in the 4 cases in whom this test was performed.

**Course and Duration.** Although even during the early febrile period there was a suggestion of abdominal localization of the disease process in all cases, this abdominal involvement became even more evident with the subsidence of the fever. Epigastric fullness, anorexia, flatulence and epigastric or right upper quadrant abdominal

the end of 3 weeks. At this time bed rest was abandoned, in spite of the fact that abnormal bromsulfalein retention persisted. One continued to show impairment of liver function at 10 weeks, but returned to an apparently completely normal state at 20 weeks. In the sixth patient no clinical observations were made beyond the first week of the disease.

In the remaining 3 cases the course was so prolonged as to be regarded as subacute or chronic. In one of these

TABLE II - Initial Laboratory Findings

Case	WBC	Differential					Urine Urobilin- ogen	Brom- Sulfalein	Cephalin Floccula- tion	Thymol Turbidity
		P o l y m p	L m	M n	E o s s	B a s s				
J.R.	7,000	58	29	8	5	0	1-160	80%	3	6 U
M.H.	5,950	57	34	7	1	1	1-320	18%	2	4 U
G.M.	4,800	44	44	10	0	2	1-40	20%	3	3.6 U
A.F.	4,500	82	17	1	0	0	1-160	18%	1	4 U
J.B.	7,800	54	38	2	6	0	1-160	12%	1	5.8 U
I.H.	7,000	50	41	6	2	1	1-320	10%	4	1.5 U
W.B.	9,000	62	30	3	5	0	1-80	---	3	6 U
J.E.	Not done	Not done					1-60	4%	3	4 U
R.B.	6,400	46	50	3	1	0	1-160	---	3	4 U

tenderness were prominent. These symptoms, while not severe, were persistent and troublesome. It was consistently noted, furthermore, that early abandonment of bed rest led to an increase in intensity of these symptoms; while return to bed rest resulted in abatement.

In 3 of the cases, maintenance of a high caloric, high protein diet and bed rest resulted in complete disappearance of all signs, symptoms and laboratory abnormalities. This required 5, 6 and 8 weeks respectively. Two patients were free of signs and symptoms by

patients there was present excessive fatigability, anorexia, abdominal fullness and weight loss as well as impaired liver function at the end of 20 weeks. Another patient showed similar symptoms, as well as impaired bromsulfalein excretion at the end of 4 months. In the last case persistent fatigability, right subcostal pain, epigastric fullness and anorexia remained for 5 months before disappearing. In this case liver function studies were normal by the sixth week.

**Discussion.** Though most of the criteria given above are not specific

for anicteric hepatitis, when considered as a whole, they afford a good diagnostic clinical picture.

The cases presented in this study satisfy the major criteria for the diagnosis of this disease. Also all showed evidences of hepatic involvement both by physical signs and laboratory studies after the febrile period was over. This is worthy of emphasis since fever alone can produce transient impairment of liver function<sup>7</sup>. The persistence of evidence of hepatic damage long after the febrile period is therefore suggestive of a specific effect of the disease in the liver. Further evidence that this was a form of hepatitis is given by the improvement of these patients on bed rest and diet, as well as exacerbation on exertion. It is significant that in 4 of the 9 cases the course was extremely prolonged. When last seen, 2 of the patients still had laboratory evidence of impaired liver function and symptoms suggesting chronic hepatitis. While in some of the cases all of the laboratory tests of liver function did not show parallel degrees of impairment, in all cases one or more of the tests used did show liver damage. This is a state of affairs we might expect, for were the liver damage sufficiently severe to produce marked, consistent impairment by all tests used, we would also expect bilirubin retention, *i. e.* jaundice.

The cause of the anicteric hepatitis noted in these patients was not determined. That it was the virus of infectious hepatitis or an allied strain can neither be stated nor denied. It is likely, however, that the etiological agent was a virus in view of the early clinical features. It has been stated that the virus of primary atypical pneumonia or of infectious mononucleosis may also cause an infectious hepatic injury with or without jaundice. It is conceivable that other viruses may also at times involve the liver. It is,

however, relatively unimportant clinically whether liver damage in the presence of acute infectious disease is caused by a virus which is primarily and usually hepatotropic, as in infectious hepatitis, or whether the hepatic dysfunction is a less frequent component of a systemic disease. It is reasonable to believe that when the liver is sufficiently involved for hepatic dysfunction to be clinically manifest, the treatment should be the same as for a primary hepatitis. The evidence of liver damage in the apparently non-specific systemic syndromes described in this paper, and the demonstrated propensity of such liver damage to become chronic, point to the importance of recognizing sporadic cases of anicteric hepatitis and instituting proper treatment if chronic hepatitis is to be averted.

It was pointed out by Budd<sup>5</sup> in 1846 that infectious hepatitis can occur without jaundice. Esler<sup>11</sup>, in 1902, likewise, emphasized the occurrence of non-icteric cases during epidemics of jaundice. Cockayne, in his classic review of sporadic and epidemic catarrhal jaundice, included in the clinical description the possibility of anicteric cases. In the study of Jones and Minot<sup>16</sup>, in 1923, it is stated that "mild cases" without jaundice are especially prone to occur during epidemics. These observers, as well as others<sup>12,14,19,23,35</sup> who have discussed infectious hepatitis more recently, apparently regarded the occurrence of anicteric cases as of interest only in demonstrating the wide variation in intensity that can occur diagnosing infectious hepatitis without jaundice and to comment on the high incidence of this form of the disease. The observations of these authors have not only been corroborated by reports of other wartime epidemics, but have been further validated by the experimental induction of anicteric hepatitis in volunteers<sup>23,28</sup>.

Although the need for recognizing sporadic cases of anicteric hepatitis has recently been emphasized, and the criteria elaborated<sup>7</sup>, there have been no clinical reports of cases of hepatitis without jaundice diagnosed in the absence of an epidemic of infectious hepatitis with jaundice. It has been noted that the clinical picture of anicteric hepatitis differs in no significant respect from pre-icteric cases which ultimately develop jaundice<sup>2,14,35</sup>. Evidence of a systemic infection, with fever, chilly sensations but rarely frank chills, and frontal headache when combined with preponderant anorexia and abdominal discomfort should suggest the possibility of anicteric or preicteric hepatitis. If the abdominal discomfort localizes in the epigastrium or right upper quadrant, the likelihood is increased. Tenderness in the right upper quadrant or epigastrium, with or without hepatomegaly, is the only helpful physical sign. In this connection, it should be emphasized that instead of true tenderness, there may be a "queasiness" or mild nausea induced by compression of the epigastrium. The diagnosis, when suspected, is confirmed by the demonstration of impaired liver function after the fever has disappeared. Capps and Sborov<sup>7</sup>, conclude from extensive experience during the recent war, that the quantitative urine urobilinogen, cephalin flocculation and bromsulfalein retention tests are of the greatest value for this purpose. These workers suggest that inclusion of the thymol turbidity test might also be of aid. Demonstration of hyperbilirubinemia or of bilinuria would obviously be of even more specific diagnostic value, although not essential for the diagnosis of anicteric hepatitis.

In 1923, Jones and Minot<sup>16</sup> suggested that occasionally infectious hepatitis may result in cirrhosis. During the last decade there has been ample confirmation of this possibility. Bloomfield<sup>4</sup> in

1938, found that of a group of patients with cirrhosis of the liver, approximately ten per cent had had an episode of acute jaundice years before. Several years later, Kornberg<sup>18</sup> reported that patients who had apparently recovered from catarrhal jaundice showed as a residuum, long-standing impairment of the liver function often associated with a suggestive symptom complex. Altschule and Gilligan<sup>1</sup>, likewise, found abnormal liver function years after the original attack, although, they regarded these sequelae as representing a "mild, benign form of chronic hepatitis". Barker and his co-workers<sup>3</sup> have given a careful description of the signs and symptoms of chronic hepatitis seen during the epidemic of acute hepatitis in the Mediterranean theatre of operations. It is their opinion that this syndrome may result in cirrhosis. From Watson<sup>15,33</sup> and other workers<sup>9,21</sup> has come clinical evidence confirming this view. Likewise histological evidence obtained by liver biopsy, has demonstrated the transition from acute infectious hepatitis to a chronic, fibrotic hepatic lesion<sup>10,31</sup>.

It has been shown that the duration of a bout of infectious hepatitis is proportional to the depth of jaundice<sup>35</sup>. It would, therefore seem that the most severe and deeply jaundiced cases would be most prone to develop prolonged and disabling sequelae. This situation is mitigated, however, by the fact that the deeply jaundiced patient, in whom the severity of illness is obvious, is most likely to receive adequate treatment. It has been pointed out<sup>6</sup>, on the other hand, that anicteric hepatitis may present a special hazard with respect to the occurrence of jaundice and the ease with which the episode might be overlooked or called "flu" or "grippe" can lead to improper handling. It is these latter cases, which, in the absence of sufficient bed rest and

a favorable diet, might develop chronic hepatitis<sup>6</sup>.

**Summary and Conclusions.** In the course of observations of apparently acute virus diseases, nine cases of anicteric hepatitis were studied. Clinical features conformed to those seen in epidemic icteric and non-icteric hepatitis. Urobilinogenuria was seen in all cases and evidence of impaired liver function as shown by brom-sulfalein retention, abnormal cephalin flocculation and thymol turbidity tests was common.

The duration of symptoms and the response to treatment were similar to

those seen in icteric hepatitis. The occurrence of a prolonged course, with the propensity to develop subacute or chronic hepatitis, has been described in two cases.

The potential of infectious hepatitis to leave disabling residua is emphasized. A similar hazard is offered by anicteric hepatitis, potentiated by the ease with which this form of the disease may be overlooked. Whenever a nondescript febrile syndrome presents itself, anicteric hepatitis should be looked for and if the clinical features are suggestive, appropriate liver function studies should be made.

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# ORNITHOSIS (PSITTACOSIS), A REVIEW

WITH A REPORT OF EIGHT CASES RESULTING FROM CONTACT WITH THE  
DOMESTIC PEKIN DUCK

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The appearance in recent years of sporadic and epidemic pneumonitis of an atypical character has resulted in the delineation of the clinical entity known as primary atypical pneumonia. The negative bacteriologic findings associated with the disease have prompted numerous attempts to isolate a causative viral agent. Findings as regards primary atypical pneumonia have been equivocal, but a number of viral agents capable of causing pneumonitis clinically indistinguishable from primary atypical pneumonia have been isolated. Certain of these agents belong to the psittacosis-lymphogranuloma group of viruses, which were the first viral agents of animal origin recognized as capable of producing pneumonitis in man<sup>38</sup>.

This report summarizes the knowledge to date concerning pneumonitis caused by the viruses of psittacosis (ornithosis) and presents 8 cases of ornithosis in man resulting from contact with a hitherto unrecognized focus of infection, the domestic Pekin duck. The initial diagnosis was made by the author in April of 1945 in an atypical pneumonia affecting a duck worker and was verified serologically soon thereafter.

Excellent summaries of the history of the disease may be found in Meyer's<sup>25,26</sup> and Favour's<sup>11</sup> articles. In recent years the findings of interest have been the isolation in animals<sup>1,2,17,18,24</sup> and in man with no known animal contacts<sup>13,21,45</sup> of members of the psittacosis group of viruses. Of these, the virus isolated by Baker<sup>1,2</sup> is the only

one of mammalian origin believed able to produce infection in man. An ornithotic virus has been identified by Pollard<sup>37</sup> in marine birds. The prediction by Meyer<sup>27</sup> and Meyer and Eddie<sup>28</sup> that barnyard fowl may be a reservoir of ornithosis is fulfilled in this communication in which all but one of the clinical cases were in intimate contact with the domestic duck. These birds are grown in tremendous numbers (7 million annually) on a number of farms located in the eastern end of Long Island. The association between human pneumonitis and occupational exposure was recognized and diagnosis verified by complement fixation tests. Subsequently an ornithotic virus was isolated from the ducks by Drs. K. F. Meyer and B. Eddie of the University of California. This will be the subject of a future communication.

**Review of Psittacosis - Ornithosis.**  
*Definition:* Psittacosis is a specific disease of birds of the parrot family that is highly communicable to man. Ornithosis is the name given by Meyer to similar infections in birds other than those of the parrot family.

*Epidemiology.* Psittacosis-Ornithosis is essentially an endemic disease in a variety of wild and domesticated birds which, under certain circumstances, may become epidemic. The work of Meyer and Eddie<sup>25,29,30</sup> on domesticated birds and of Burnet<sup>6,7</sup> on birds in a wild state indicates that the infection is transmitted to the young in the nest, either by parents who are shedders of the virus or

through activation of latent infection in the breeding female. The mortality of the infection so acquired is low; excretion of the virus in droppings and nasal discharges ceases in most birds after several months. The virus, however, remains latent in the spleen and other organs and may become activated by adverse environmental conditions. Relapses, therefore, may occur in which excretion of the virus recurs. Human infection follows contact, fleeting or intimate, with infected birds. Such infections, as a rule, follow acquisition of the birds by a few weeks<sup>26</sup>. Visitors to the infected person may become infected, and this accounts for the characteristically localized epidemics of the disease. Transmission to man occurs in one of 2 ways; more commonly by inhalation of dust containing virus particles originating in droppings or nasal secretion from infected birds, less commonly the infection is acquired by the bite of an infected bird. The majority of clinical cases occur in adults. Children under 10 years of age appear to be much less susceptible to infection and, as a rule, run a much milder clinical course. The opinion that psittacosis is invariably severe and associated with a high mortality rate has been modified in recent years. While the classical disease is still associated with an appreciable mortality rate, the mortality following infection by related ornithotic strains of virus tends to be lower. Numbers of individuals exposed to infection in birds never develop clinical manifestations but they do show, as evidence of previous infection, high titers of complement fixing antibodies in their serum. This will be discussed in a future communication.

Human-to-human spread has been limited by the necessity for contact with an actual case and has been reported about 30 times, usually in

nurses or doctors attendant upon patients. Since Gerlach's<sup>14</sup> demonstration of virus in the sputum of 4 individuals who lacked clinical symptoms of psittacosis, the possibility of a human carrier state has been known to exist. Meyer and Eddie's recent report<sup>31</sup> of an individual whose sputum harbored virus 8 years after recovery from psittacosis is of particular interest, since it is one step further along the course the disease may take to become a disease of man. While no cases have been traced to contact with this human carrier, it is conceivable that a mutant strain capable of infecting contacts and established in carriers, may arise in the future and alter the ecology of the disease. This potentiality has been emphasized by both Burnet<sup>8</sup> and Smadel<sup>41</sup>.

*Etiology.* The filterability of the causative agent was established independently and in rapid succession by a number of investigators during the pandemic of 1929, 1930<sup>3,19,20,22,42</sup>. Two discoveries have been of inestimable value in the laboratory and in clinical investigation of the disease. The first was the work of Krumwiede<sup>27</sup> and of Rivers and Berry<sup>40</sup> which showed that diagnosis could be made by growing the virus from infected material by injecting the material into the white mouse. The other was the work of Bedson<sup>5</sup> which showed that complement fixing antibodies appeared during the disease. The causative virus is a member of an interesting group of organisms intermediate in morphology and metabolism between the true viruses on the one hand, and bacteria and rickettsia on the other. The members of this group have staining qualities and may be seen with ordinary microscopy and thus resemble bacteria. They further resemble bacterial organisms in being susceptible to the action of sulfonamides and of penicillin. Thus

the virus of lymphogranuloma venereum is susceptible both in the laboratory and clinically to the action of sulfonamides, and members of the psittacosis-ornithosis group to the action of penicillin. The relationship between the members of the latter group is not yet clear. They may be variant forms of each other, or the descendants of a common strain modified by residence in different animal hosts. While complement fixing antibodies appear with infection by many of the members of this group, differentiation by this means is impossible because of cross-reactions. Differentiation is possible solely through consideration of the source of the virus and the difference in the effects produced by various members of the group on experimental animals and birds.

*Incidence.* Earlier work led to the belief that atypical pneumonias caused by agents of this group were relatively common<sup>9,39</sup>. More recent work relegates psittacosis (ornithosis) to a minor position as a factor in the causation of atypical pneumonia<sup>10</sup>. On the other hand, the steadily increasing number of animal reservoirs of viruses of this group, and the demonstration of the carrier state in man warrants constant consideration of the possibility of psittacosis-ornithosis in all atypical pneumonias.

*Morbid Anatomy.* The principle findings in man are in the lungs. These show a diffuse confluent bronchopneumonia which starts at the hilum and extends to the periphery. Pleural involvement is rare and bronchitis uncommon unless there is secondary bacterial infection. Microscopically, the alveolar walls show marked mononuclear infiltration, and the alveolar spaces are filled with a monocytic exudate and alveolar epithelium which is characteristically thrown into folds of proliferating cuboidal cells. Secondary

invasion by the pneumococcus or streptococcus may alter the picture. The liver shows fatty degeneration and areas of focal necrosis. The spleen may be enlarged and at times show hyaline degeneration of the smaller vessels<sup>23,26</sup>.

*Incubation.* In general the incubation period varies from 7 to 15 days, although in some cases it has been much longer (up to 30 days). After the bite of a parrot a 30-day incubation period has been reported.

*Symptoms and Signs.* The initial symptoms are those associated with any infection and resemble more particularly those of influenza. There is headache, photophobia, sweating, malaise, anorexia and abdominal distention. A characteristic finding is a relatively slow pulse. In cases of usual severity the fever is continuous and lasts for 3 or 4 weeks. Defervescence is by lysis in those cases that recover spontaneously. Physical findings are confined to the lungs which show a variety of changes. These vary from diffuse or patchy areas of pneumonitis without consolidation to areas of focal consolidation in one or both lungs. An outstanding feature of the pneumonitis is the paucity of complaints referable to the respiratory tract. Dyspnea and tachypnea are rare, despite evidences of widespread pulmonary involvement. Cough may be slight or absent, and sputum scarce or mucoid. Roentgen-ray findings are positive before there is any evidence on physical examination that pulmonary involvement is present. They precede physical signs by several days and initially are confined to the hilar regions and to the peribronchial areas centrally. In a few days the infiltration spreads peripherally, and signs of consolidation and focal infiltration of the parenchyma appear. Physical signs of pneumonitis may (as in some of the cases to be presented) be evident, and



Roentgen-ray findings appear minimal. In our cases there was no correlation between the clinical severity of the illness and the degree of pulmonary involvement on examination or roentgenogram. Several cases with a moderate clinical picture, and one severely ill patient, showed only peribronchial infiltration on roentgenogram.

Convalescence following recovery is usually prolonged and relapses are not infrequent.

Complications are few. Myocarditis and peripheral thromboses have been reported.

Death results from toxemia or pulmonary insufficiency. The severity of the clinical picture is dependent on a number of factors. Age and associated changes tend to favor a severe illness. There is also some variation in the clinical severity of the infection with the different members of the psittacosis-ornithosis group. The ornithotic strain present in our patients caused predominantly moderate clinical illness. Favour<sup>11</sup> classifies the cases into 3 groups, depending on their severity. The first group is composed of mild cases with influenza-like illness and a short course. The second group comprises cases of moderate severity with typhoidal state, pneumonia, and a course of 3 to 4 weeks duration. The third group is composed of cases with marked toxic manifestations, widespread pneumonia and a longer course. These, as a rule, appear in older individuals and in those with an underlying disease. Cyanosis appears early. Delirium and stupor are prominent. Encephalitic symptoms may appear and myocardial damage become evident. Relapses are frequent and the mortality rate high. This classification will be followed in the presentation of the cases reported in this communication.

*Diagnosis.* Clinical differentiation between psittacosis-ornithosis, primary

atypical pneumonia, influenza and typhoid fever may be extremely difficult. A history of contact with birds of any type may be helpful. The unusual association of extensive pneumonitis without dyspnea or much cough may be significant, as may the bradycardia. Essentially, the diagnosis is made by laboratory procedures. Negative stool cultures and a negative Widal help to eliminate typhoid fever. Absence of cold agglutinins and a negative agglutination reaction for streptococcus MG help to eliminate primary atypical pneumonia. Failure to isolate virus and a negative complement fixation reaction serve to eliminate influenza. Positive findings in psittacosis-ornithosis are of 2 types. The first is absolutely diagnostic, and follows inoculation of a white mouse with blood (which contains virus from a 1 to 3 day illness) or sputum obtained from a 5 to 23 day course of the disease<sup>26,40</sup>. Characteristic changes in the organs of the mouse follow, and identification of the virus in the tissues is possible by ordinary microscopy. The second positive diagnostic procedure is the complement fixation reaction. Complement fixing antibodies appear in the serum on about the 8th day of illness, and a significant rise in titer above the 8 day level on the 15th day is considered diagnostic. Similarly, an elevated titer during illness followed by a fall early in convalescence is suggestive. Single determinations, if high, may be helpful. The titer is considered to be within diagnostic levels if it reaches a dilution of 1:16 (4 plus)<sup>5,33</sup>.

*Prognosis.* As knowledge concerning the disease has accumulated, the original estimate of a mortality of 30 to 40% has fallen considerably. An average mortality estimate of 10% is more likely to approximate the truth. It is not unlikely that certain strains

of virus cause even a lower mortality rate.

*Treatment.* Despite some experimental evidence that large doses of sulfadiazine may inhibit growth of the viruses of this group, its clinical use in human infections has been disappointing<sup>43</sup>. Penicillin has been shown to be efficacious in experimental infections of mice<sup>4,15,16</sup>, and has been reported as influencing favorably infections in man<sup>12,31,36,44</sup>. In the mouse, relatively enormous doses must be given to prevent death. Equivalent

responded to sulfonamides. This patient responded to 100,000 units daily. Meyer and Eddie<sup>31</sup> report favorable results with doses up to 300,000 units daily, and warn against discontinuing penicillin therapy too soon after deferescence in order to prevent relapse.

*Case Reports.* (*Group I—Mild Illness*) CASE 1. T. H., male, aged 44, white, employed as handyman on duck farm, took sick on April 2, 1945, with chills, headache and abdominal distension. Physical examination during the first 2 days of illness was negative. His tem-

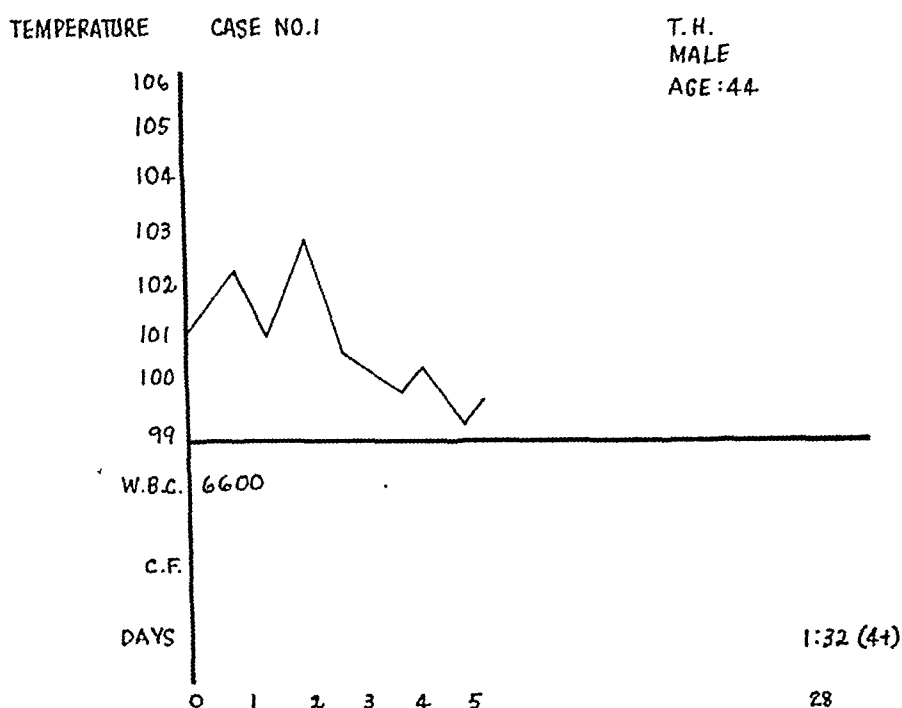


Fig. 1, CASE 1, T.H.—Clinical chart showing mild ornithotic infection of short duration with spontaneous recovery.

dosage in man would require the administration of from 3 to 11 million units daily. Despite this, favorable reports of the use of penicillin in human infection have followed the administration of from 80,000 to 300,000 units daily. Thus Parker<sup>36</sup> used 120,000 units daily rather late in the course of the disease, and was impressed by the favorable response. Flippin *et al.*<sup>12</sup> report definite benefit in a patient who had been ill for 19 days and had not

perature varied from 100.2° to 102°. The pulse rate was 60. On the 3rd day of the illness fine rales were audible at the right base posteriorly. This was associated with some percussion dullness. Clinically, there was no suggestion of pulmonary involvement. The respiratory rate was not increased, and there was no cough. Because of the unusual nature of the illness and the patient's occupation, ornithosis was considered as a diagnostic possibility, and he was admitted to the Southampton Hospital on April 6, 1945, for further study. Roentgenograms

showed a patchy pneumonitis of the lower half of the right lung field. The leukocyte count was 6900 (neutrophils 69%, lymphocytes 26%, monocytes 4% and eosinophils 1%). He was given sulfadiazine in small doses; his temperature started falling on the 2nd day of hospitalization (Fig. 1), and he insisted on going home. He ran a low-grade fever for 1 week after discharge. During this time the physical findings in his chest gradually disappeared.

(Group II—Moderate Illness) CASE 2. S. B., male, aged 41, white, duck marketer, took sick on April 15, 1945, with chills, fever and malaise. These symptoms continued until admission to the Southampton Hospital on May 2, 1945. On admission he complained of headache and occasional cough. Physical findings were confined to the chest. There were numerous fine rales at both bases posteriorly. Roentgenograms (Fig. 2) showed

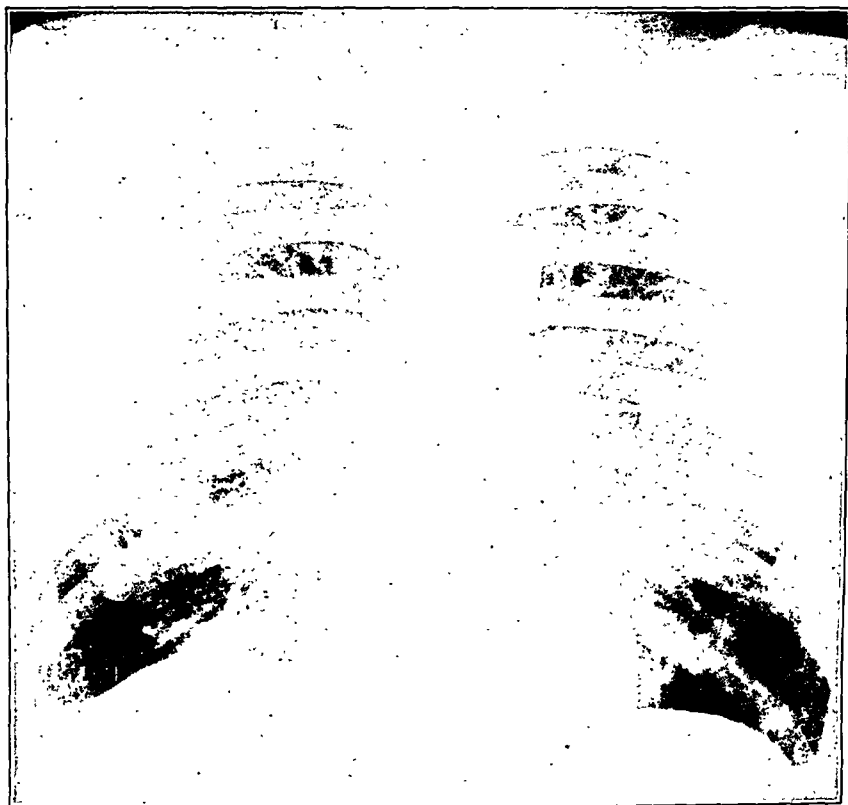


Fig. 2, CASE 2, S.B.—X-ray of chest showing, solely, exaggerated hilar markings. Film taken 2 weeks after onset of illness.

Arrangements for doing complement fixation tests with his serum were not completed until the 28th day after the onset of the illness. Serum taken on that day showed a titer of 1:32 (4 plus).

*Comment.* This case is of particular interest because of the mild symptoms and short course. The chest findings were incidental to symptoms of an influenza-like nature and could readily have been missed.

exaggerated hilar markings on the inner thirds of both lung fields. The leukocyte count was 9300 (neutrophils 87%, lymphocytes 13%). On admission sulfadiazine was given in doses of 1 gm. every 4 hours. This was continued for 2 days and then stopped, for there was no improvement. Penicillin was then started. The initial dosage was 25,000 units, intramuscularly, every 3 hours. There was no improvement. After 2 days the dosage of penicillin was increased to 50,000 units.

every 3 hours. There was a prompt response. His temperature fell to normal within 24 hours. Complement fixation done on the 12th day of illness showed a titer of 1:16 (4 plus). The test was repeated on the 30th day and the level was again 1:16 (4 plus).

*Comment.* This patient failed to respond to sulfadiazine and to penicillin in a dosage of 200,000 units daily.

Southampton Hospital on April 30, 1945. She had taken sick the previous day with chills, sweats and headache. The diagnosis on admission was atypical pneumonia. Physical findings were confined to the left supraclavicular area. Roentgenograms (Fig. 3) on admission showed a bronchopneumonia of the left upper lobe and increased hilar markings. The leukocyte count was 7950 (neutrophils 73%, lymph-



Fig. 3, CASE 3, E.A.—X-ray of chest taken day after onset of illness showing bronchopneumonia of left upper lobe and increase in hilar markings.

Of interest, however, is the fact that he responded promptly to a dosage of 400,000 units of penicillin daily. Because of the prompt response to adequate penicillin therapy, we determined to treat future cases with 400,000 units daily, as soon as the diagnosis was suspected.

CASE 3. E. A., female, aged 49, colored, duck picker, was admitted to the

ocytes 37%). Treatment consisted of sulfadiazine gm. 1, every 4 hours. This was given for the first 4 days after admission and then discontinued because there was no response. Fever continued for 5 more days and was followed by defervescence and recovery (Fig. 4). Inasmuch as she had left the hospital before the complement fixation on the first case was reported, no blood was taken until the 14th day of her illness and peni-

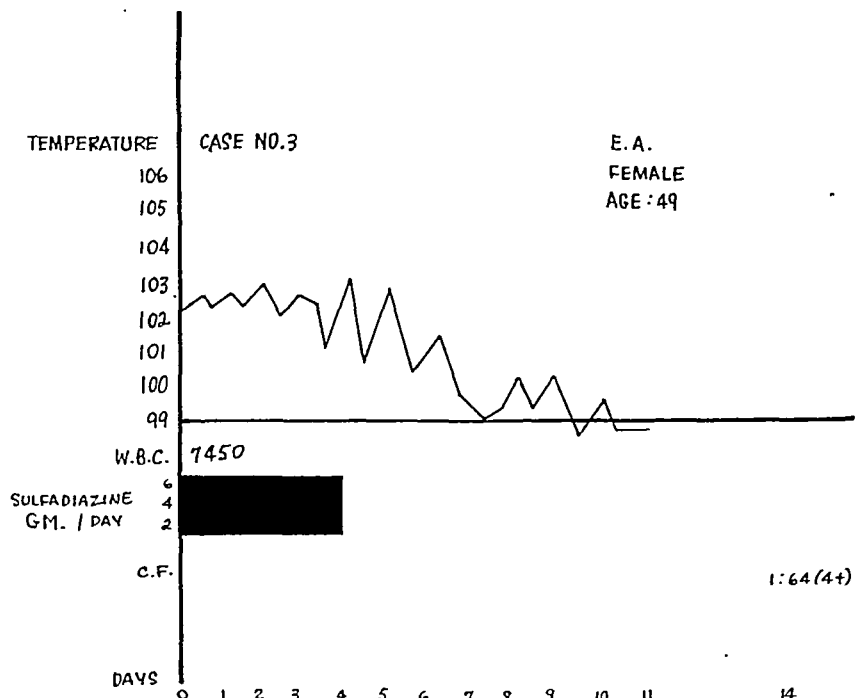


Fig. 4, CASE 3, E.A.—Clinical chart of case of moderate severity showing lack of response to sulfadiazine and spontaneous recovery after a febrile course of 1 week.

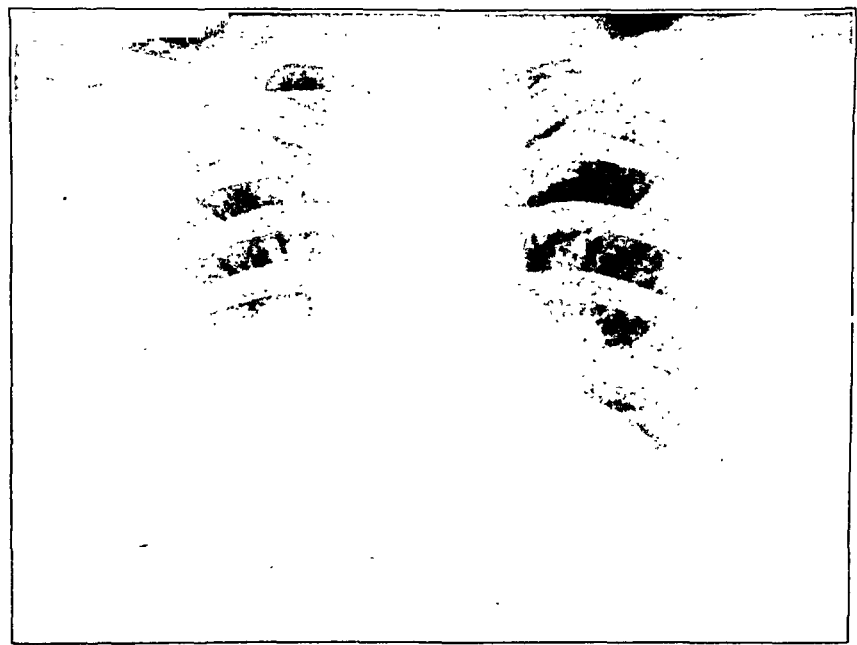


Fig. 5, CASE 4, A.N.—X-ray of chest in case of moderate clinical severity taken 8 days after onset showing a patchy pneumonitis in the right hilar area.

cillin was not administered. Complement fixation titer was reported as 1:64 (4 plus).

*Comment.* This patient also demonstrates the lack of response to sulfadiazine. The illness was of moderate severity, and there was spontaneous recovery after a febrile course of about 9 days duration.

CASE 4. A. N., female, aged 46, white, duck picker, took sick on May 22, 1945, and was treated symptomatically at home until May 29, 1945. On that date she was admitted to the Southampton Hospital with the diagnosis of primary atypical pneumonia. Her complaints were pain in

*Comment.* This case demonstrates a prompt response to penicillin in doses of 50,000 units every 3 hours.

CASE 5. S. D., female, aged 44, colored, duck picker, took sick on May 17, 1945, and was treated symptomatically at home until June 1, 1945, when she was admitted to the Southampton Hospital with the diagnosis of primary atypical pneumonia. She complained of pain in the chest, cough, fatigue and headache. Examination on admission showed dullness over the right upper and middle lobes, with rales over these areas and over both bases. Roentgenogram showed a patchy

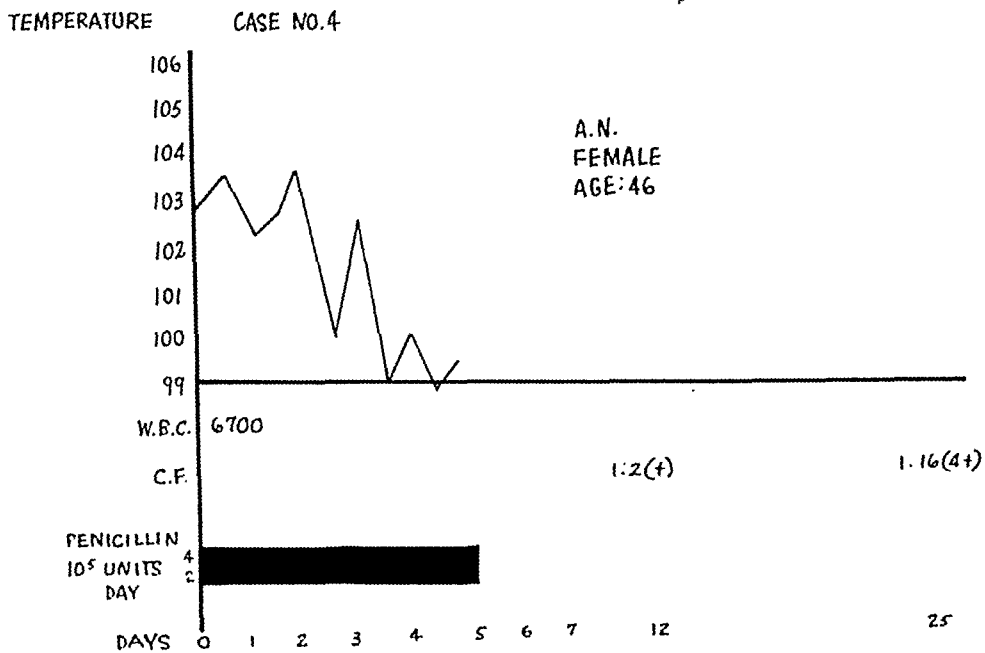


Fig. 6, CASE 4, A.N.—Clinical chart showing prompt response to penicillin 400,000 units daily.

the chest, chills, fatigue and headache. Physical examination on admission revealed sibilant rales throughout both lungs. Roentgenogram (Fig. 5) showed a patchy pneumonitis in the right hilar area. The leukocyte count was 6700 (neutrophils 79%, lymphocytes 19%, monocytes 2%). Penicillin was started on admission, being given in doses of 50,000 units, intramuscularly, every 3 hours. Her temperature fell to normal on the 3rd hospital day (Fig. 6). Serum taken on the 12th day fixed complement in a dilution of 1:2 (1 plus). On the 25th day serum fixed complement in a dilution of 1:16 (4 plus).

bronchopneumonia of both bases especially the right. The leukocyte count was 9700 (neutrophils 56%, lymphocytes 42%, monocytes 2%). Penicillin was started promptly on admission in the dosage we had established as being adequate in the previous cases (400,000 units daily). There was no response, although the penicillin was continued for 5 days. This was followed by sulfadiazine in an initial dose of 3 gm., with subsequent doses of gm. 1, every 4 hours. Her temperature fell to normal after 48 hours (Fig. 7), but the contribution of the sulfadiazine to her recovery is questionable. Complement fixation test with serum taken on the 10th

day of illness showed a titer of 1:128 (4 plus).

*Comment.* The failure of this patient to respond to penicillin is of interest. She may have had a mixed infection with a bacterial organism that responded to sulfadiazine and not to penicillin, or it may have been necessary to have given even larger doses of penicillin in her case to cause recovery. Theoretically, she might have had a viral pneumonia other than that of ornithosis, and the complement fixing

mission she was given 50,000 units of penicillin, intramuscularly, every 3 hours. There was a prompt clinical improvement. Her temperature fell to normal after 48 hours. Her course in the hospital was complicated by recurring epistaxis. Complement fixation tests done with serum taken on the 7th day of illness showed fixation in a dilution of 1:16 (4 plus). Serum taken on the 20th day showed fixation in a dilution of 1:128 (4 plus).

*Comment.* This patient responded dramatically to 400,000 units of penicillin daily. There was no evidence of

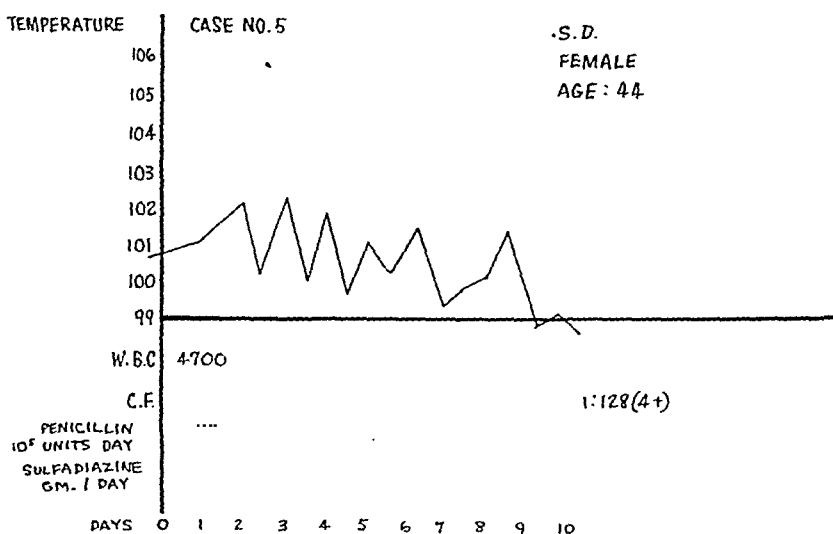


Fig. 7, CASE 5, S.D.—Clinical chart showing lack of response to penicillin 400,000 units daily. Defervescence during treatment with sulfadiazine.

titer may have arisen as an anamnestic reaction. The latter possibility seems unlikely, since the background and clinical picture resembled that of the other cases.

CASE 6. P. P., female, aged 31, colored, duck picker, took sick on May 31, 1945, with headache, pain in the back, fatigue and cough. She was treated symptomatically at home, and admitted to the Southampton Hospital on June 3, 1945. Positive findings were confined to the lungs, which showed fine rales at both bases posteriorly. X-ray showed moderate accentuation of hilar markings and a prominent bronchial tree. The leukocyte count was 5500 (neutrophils 66%, lymphocytes 32%, monocytes 2%). On ad-

pulmonary consolidation, either on physical examination or X-ray.

CASE 7. E. S., female, aged 47, white, housewife, owned ducks and lived a short distance from a plant in which ducks were processed for market. She took sick with fever, fatigue and cough on May 19, 1945. She was treated symptomatically at home until June 5, 1945, when she was admitted to the Southampton Hospital for further study. Positive findings were limited to the lungs which showed fine rales at both bases, and dullness to percussion over both lower lobes. Roentgenogram showed evidence of an acute upper respiratory infection. The leukocyte count was 12,300 (neutrophils 81%, lymphocytes 18%, monocytes 1%). Penicillin was given in

doses of 50,000 units intramuscularly, every 3 hours, for 4 days with no response. The patient developed erythema nodosum during this time. On the 5th day, sulfadiazine was started in doses of gm. 1, every 4 hours. Her temperature fell to normal rather promptly following this, and her clinical condition improved. The effect of the sulfonamide is difficult to evaluate, since it was given only in moderate dosage and for a short time. Complement fixation tests, done on the 16th day, showed a titer of 1:64 (4 plus).

*Comment.* This patient did not respond to 400,000 units of penicillin

daily. X-ray showed no signs of pneumonitis. The same theoretic considerations are present in this case as in Case No. 5.

*Group III—Severe Illness.* CASE 8. E. Sc., female, aged 71, white, housewife, did not own ducks, but in February of 1945 had visited on a duck farm, and in March and April was confined to bed with pneumonia, for which she received sulfadiazine. Had been feeling poorly since then, and on June 12, 1945, took sick again with fever, cough, expectoration and an eruption on her hands and back. She was admitted to the Southampton Hospital on

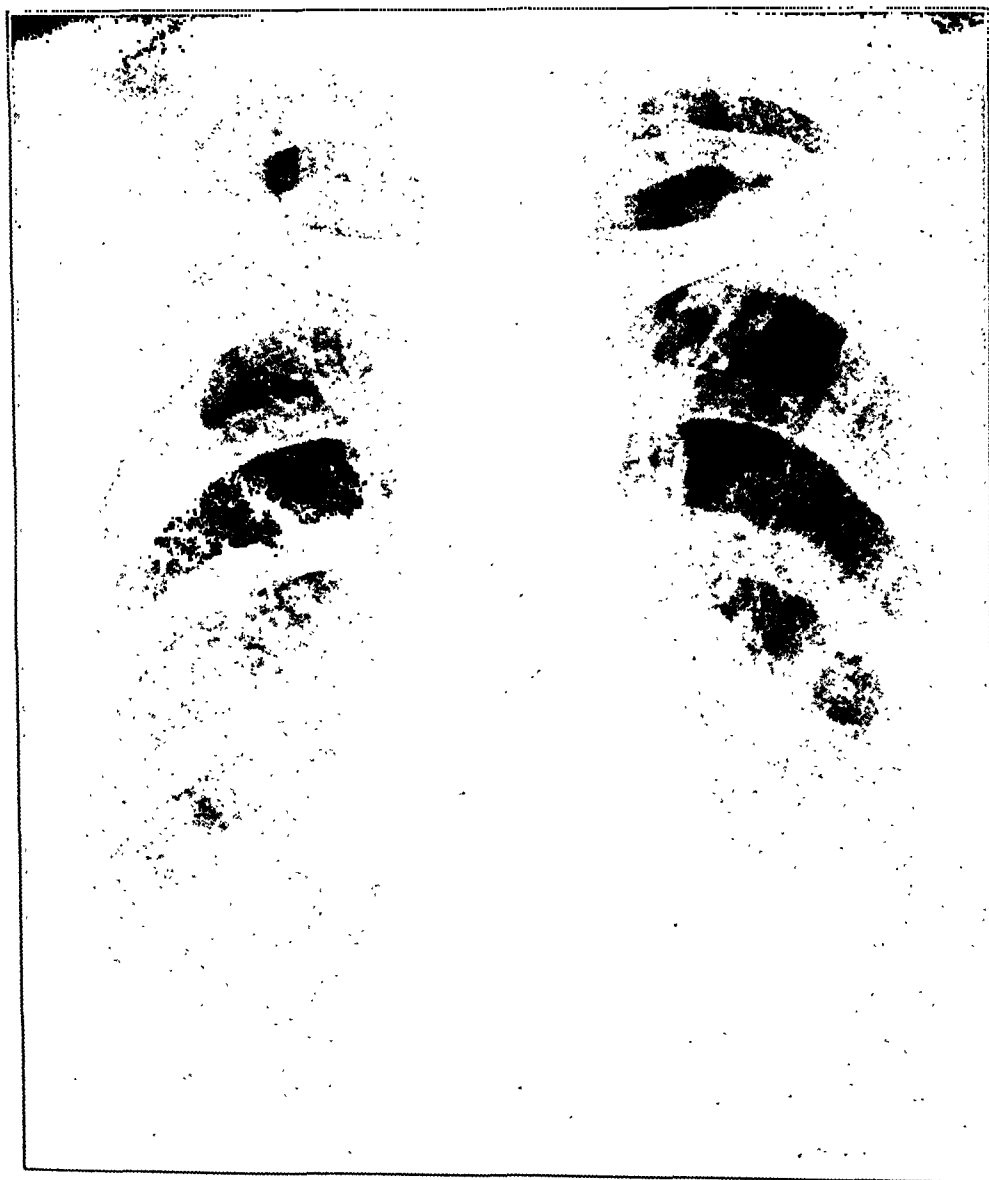


Fig. 8, CASE 8, E.Sc.—X-ray of severely ill patient taken on 1st day of illness (relapse) showing increase in hilar markings.



that day. Examination revealed an elderly white female, who was acutely ill. She was coughing frequently and productively, and raising a whitish, mucoid sputum. Examination of the chest showed dullness to percussion in both interscapular areas. On the palms of both hands and on her back there were purplish-red plaques that were slightly elevated and extremely pruritic. During the next few days her condition deteriorated and became critical. Her mental status varied from confusion to somnolence. Cough and the itching of the hands was distressing. Roentgenograms (Fig. 8) on admission

illness, showed positive fixation in a titer of 1:64 (4 plus).

*Comment.* This patient was by far the most ill of the 8 presented, possibly because of her age. It seems very likely that the illness was a relapse of an original infection in March and April of 1945. Pulmonary changes on physical and Roentgen-ray examination were few.

*Discussion.* The ornithotic infection in these individuals is of considerable epidemiologic interest. The

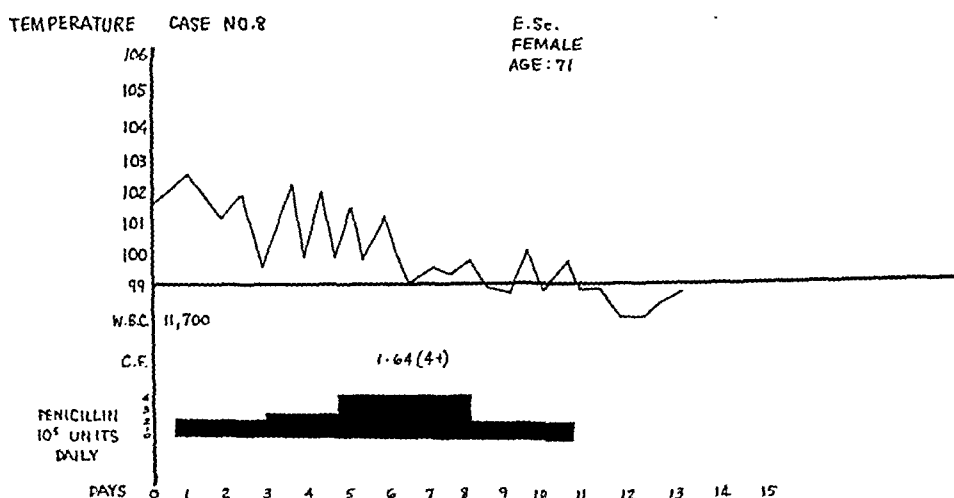


Fig. 9, CASE 8, E.Sc.—Clinical chart of severely ill patient showing lack of response to penicillin 150,000 units daily and 200,000 units daily, with prompt response to doses of 400,000 units daily.

showed an increase in hilar markings. The leukocyte count was 11,700 (neutrophils 37%, lymphocytes 63%). Her course was extremely interesting. She was given penicillin in doses of 25,000 units every 4 hours on admission, and after 3 days with no improvement, the dose was increased to 25,000 units every 3 hours. Nevertheless, her condition continued critical. Two days later the penicillin was increased to 50,000 units every 3 hours. Following institution of this dosage, her improvement was dramatic. Her mental status cleared, the cough diminished rapidly in severity and frequency, and her temperature began to fall, reaching normal in 48 hours (Fig. 9). Complement fixation tests, done with serum taken on the 6th day of

infection in the ducks was shown subsequently to be of an endemic nature. In consequence, most of these individuals had been exposed to ornithotic infection for years and had thus apparently acquired sufficient immunity to remain well until their present illness. The seasonal onset (April and May) of most of the illnesses is important in attempting to explain the loss of immunity. The fact that duck growing is at a minimum in cold weather and the first ducks marketed are killed in March suggests the factors responsible for the onset of the illness. It would seem that individuals who

have lost sufficient immunity after some months without contact with ducks, on again being exposed to infection, develop clinical illness. Only a small percentage, however, of those employed on the farms lose sufficient immunity to become susceptible. This sequence of events, which is a re-infection rather than an illness after an initial exposure, may account for the generally mild nature of the disease, since an accelerated immune response under such circumstances is to be expected. That infection in other workers without any history of illness is widespread is evidenced by the finding of complement fixing titers within diagnostic levels in 37% of duck workers, as contrasted with similar levels in only 3.4% of the general population locally.

In harmony with the generally mild character of the disease locally is the type of pulmonary change found on Roentgen-ray and physical examination. Several of the patients had minimal hilar changes indistinguishable from those of other upper respiratory infections. Others had some hilar infiltration and peribronchial thickening. These findings were not necessarily limited to early cases. In this respect it appears that ornithosis may resemble in behavior other viral infections of the respiratory tract which are capable of producing all degrees of pulmonary involvement from minimal changes to extensive pneumonia.

The response to penicillin in 4 of 6 patients who were given 400,000 units

daily was prompt and left little doubt as to its efficacy in such dosage. The failure of the penicillin to affect the other 2 cases, who showed defervescence after penicillin was stopped and sulfadiazine started, is difficult to explain unless it be assumed that the dosage was inadequate or that a mixed infection was present. There is no evidence that administration of penicillin for more than the usual time after defervescence is necessary to prevent relapse.

**Summary.** 1. Psittacosis-ornithosis is reviewed clinically, and 8 cases resulting from contact with infected domestic ducks are reported.

2. Mild or moderate illness predominated and there were no deaths.

3. Evidences of a frank pneumonic process are not necessarily the accompaniment of infection, nor is there any direct correlation between the severity of the illness and the changes in the chest.

4. The epidemiologic background of the clinical material suggests that immunity to ornithosis develops in many individuals after long exposure or latent infection, and that the immunity so acquired may wane unless there is constant re-exposure.

5. Penicillin in doses of 50,000 units every 3 hours was sufficient to produce prompt recovery in 4 out of 6 patients.

6. There is no evidence that penicillin must be continued for some days after defervescence to prevent relapse.

Note: The author wishes to thank Drs. K. F. Meyer and B. Eddie for the serologic examinations, and Drs. E. Bellows and J. Kris for permission to report on their patients.

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## POSTVACCINAL ENCEPHALITIS A REPORT OF 45 CASES IN NEW YORK CITY

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IN March 1947 a case of smallpox occurred in New York City, in an American business man who had recently returned from Mexico. The case was not recognized during life and isolation was not enforced until shortly before death. Seven secondary cases occurred within the city and 4 additional ones outside of New York City.<sup>9,24</sup> Since a considerable number of the population had been exposed it was considered wise to urge vaccination on all city residents. Within a period of about a month, approximately 5 million people were vaccinated.<sup>9</sup> It was realized that there existed the known risk of encephalitis following vaccination, but it was felt that the risk of smallpox was the greater one. Only 2 years before, smallpox was introduced into the Puget Sound area of Washington by a returning soldier, and, before a vaccination campaign got under way, 65 cases of smallpox with 20 deaths resulted.

Soon after the termination of the vaccination program and for 2 months thereafter, all reported cases of encephalitis, poliomyelitis and other neurotropic diseases were carefully investigated. In addition, a canvass was made of the hospitals in the city, and all cases admitted in which a diagnosis of encephalitis or postvaccinal complication

was made were checked. Furthermore, all death certificates were scanned and those in which a primary or secondary diagnosis of encephalitis was made or in which there was any indication of a complication following vaccination were likewise investigated. Finally, all cases referred to the Division of Acute Infections of the Central Nervous System were examined and those showing symptoms or signs of encephalitis following a recent vaccination were added to the list.

It should be stated in the beginning that a diagnosis of postvaccinal encephalitis made on clinical grounds is a presumptive diagnosis. Not only is there no difference between the clinical picture of this disease and that of other encephalitides, but there is often little to distinguish it from cases of tumor of the brain or of tuberculous meningitis. Of the cases on our list in which the diagnosis of postvaccinal encephalitis was made ante mortem, 2 were shown at post mortem to have been cases of tuberculous meningitis, 1 of brain tumor and 1 of hypertensive vascular disease with coronary occlusion and congestion of the brain. Armstrong<sup>2</sup> prefers the term post vaccination encephalitis to that of postvaccinal encephalitis because it connotes a temporal rather than

\* The estimate of 5,000,000 vaccinations is based on the amount of vaccine distributed by the Health Department. This was sufficient for 4,641,033 vaccinations. Part of this was in points and part in bulk, the latter in vials sufficient for 50 vaccinations. The amount of vaccine on hand in doctors' offices, drug stores and supply houses at the beginning of the campaign is not known. Many doctors used a vial for more than 50 vaccinations, often for twice that number. The estimate of 5,000,000 vaccinations is conservative.

a causal relationship between the vaccination and the disease. The latter term, however, is used so widely in the literature that we have adopted it in this paper.

**Incidence.** We were able to gather 49 cases which were diagnosed as postvaccinal encephalitis. Of these 8 died and all were autopsied. Four of the cases, as already indicated, were shown to have died of a disease other than encephalitis, and were excluded. The remaining 45 were accepted as true cases.

The incidence of postvaccinal encephalitis varies greatly in different countries. The highest incidence is found in Europe, chiefly in Holland and England. Table 1 lists the recorded

North American continent no cases were reported to the Office Internationale from Canada and Mexico. In the United States, Armstrong<sup>2</sup> collected 71 cases from 1922 to 1932. The 45 cases reported by us, following 5,000,000 vaccinations, give a ratio of 1 case to 110,000 vaccinations.

The tremendous differences in rates of incidence are manifest not only in different countries, but in different sections of the same country and in different years. Thus in Holland,<sup>4</sup> variations in rates from 1 to 2180 to 1 to 53,233 are reported for different provinces, while in Austria<sup>12</sup> the cases per units of lymph distributed varied from 1 to 286,683 in 1926 to 1 to 7749 in 1929.

TABLE 1.—POSTVACCINAL ENCEPHALITIS, CASE RATES AND FATALITY RATES, FROM REPORTS IN THE LITERATURE

Country	Year	Number Vaccinated	Number of Cases	Case Rate	Fatality Rate Percent
Holland	1924-1926	495,431	123	1:4000	30
Holland	1929-1931	866,100	186	1:4656	
Holland	1927-1937	1,866,558	152	1:12,280	
England	1922-1924	2,252,939	62	1:36,337	58
England	1923-1927	4,540,548	93	1:48,823	
Austria	1925-1929	1,584,663	80	1:19,808	27
Germany	1927-1929	6,100,000	61	1:100,000	32
Switzerland	1928-1930		0	0	
Switzerland	1921-1926	1,500,000	5	1:300,000	20
Sweden		500,000	16	1:33,000	25
Norway	1921-1929		28		53
Portugal, Roumania, Mexico, Canada			No cases.		
U.S.S.R.		8 to 9 million yearly	0		0
Jugoslavia		1,670,000	0		0

cases from the literature. In Holland 3 reports for the overlapping years 1924-1926, 1924-1931 and 1927-1937 give case rates of 1 to 4,000,<sup>20</sup> 1 to 4,500,<sup>11</sup> and 1 to 12,000,<sup>5</sup> vaccinations. The Andrewes Committee<sup>18</sup> reported 93 cases in England with a ratio of 1 to 48,800. In Austria,<sup>12</sup> the ratio was 1 to 20,000 and in Germany,<sup>21</sup> 1 to 100,000 vaccinations. The Rolleston Committee<sup>7</sup> quotes the report of the Office Internationale d'Hygiene Publique, in which the ratio of cases to numbers vaccinated is given as 1 to 300,000 for Switzerland, 1 to 33,000 for Sweden and no cases for Portugal and Roumania. Nor were any cases reported in Russia where 8 to 9 million vaccinations were done yearly, nor in Jugoslavia, following 1,670,000 vaccinations. On the

In the Tyrol the ratios were 1 to 4570 in 1927, 1 to 1213 in 1928 and 1 to 641 in 1929. In Scotland, in 1942, the ratio of cases to numbers vaccinated was 1 to 6600 in Fife<sup>17</sup> and 1 to 70,000 in Glasgow.<sup>1</sup> In the United States, where the incidence of postvaccinal encephalitis is low, Armstrong<sup>3</sup> reported in 1930 the occurrence of 5 cases among 5,000 vaccinations in a city of 450,000 people, a ratio of 1 case to 1,000 vaccinations, whereas in the entire country during the 3 years 1928-1930 there occurred 41 cases, a ratio of 1 case to 350,000 vaccine points sold. No satisfactory explanation has yet been made for the high attack rates in some localities and the absence of cases in others. That it is not a property of the lymph used is shown by the fact that the same lymph

used by Levaditi to vaccinate 2,500,000 individuals in Spain did not cause a single case, whereas when used in Holland to vaccinate 40,000 persons it produced 11 cases of postvaccinal encephalitis.

**Age and Sex.** The age distribution of the 45 cases is given in Table 2. It will

TABLE 2. — AGE DISTRIBUTION OF 45 CASES OF POSTVACCINAL ENCEPHALITIS

Age	Number of Cases	Percent of Total
0-1	0	.0
1-4	3	6.7
5-9	3	6.7
10-14	4	8.9
15-19	2	4.4
20 and over	33	73.3
Total	45	100.

be noted that no cases occurred in the first year of life and that the cases in children under 15 years of age were about one-fifth of the total number. No conclusions can be drawn from these data since the age distribution of the individuals vaccinated is not known. There were many more adults than children. The number of infants vaccinated during the campaign was very small, since the vaccination of infants is a routine procedure in the city. In countries where the incidence of postvaccinal encephalitis is high, cases occur in infants, but in a much smaller ratio than in older children. In Holland, Bastiaanse<sup>4</sup> reported age distribution of cases for the years 1924 to 1927. For the first year of life it was 4.5%. It was 10% for the second year, 78% for the next four years, 7% between the ages of 6 and 12 and only one-half of 1% after that. According to Bower<sup>5</sup> the rate in Holland during the years 1924 to 1934 was about one-sixth as high in infants 1 and 2 years old as in the older age groups. Scott<sup>19</sup> collected all cases of postvaccinal encephalitis in infants up to 1930. There were 41 cases in a total of 569 for all ages in Europe, or 7.2%, whereas the average percentage of vaccinations in infancy was 34%. In general it appears from the literature that encephalitis occurs more common-

ly in children between the ages of 3 and 12.

There were 25 men and 20 women in our 45 cases. Equal distribution in the sexes was also noted in Holland<sup>4</sup> and Austria,<sup>12</sup> but a higher attack rate in women occurred in England.<sup>18</sup> Forty-two of our cases were in whites, and 3 in negroes.

**Symptoms.** The incubation period varies, according to the reports in the literature, from 2 days to a month, with an average of 10 to 12 days. Of the cases seen by us, 8 had an incubation period of 1 to 7 days; 25, 8 to 14 days; 7, 15 to 21 days and 5, 16 to 28 days. The average incubation period was between 10 to 12 days.

The clinical picture was variable. The onset, as a rule, was abrupt, with fever, headache, vomiting and changes in the mental state. In a few cases the initial symptoms were followed by a period of remission lasting 24 to 72 hours, after which symptoms continued to progress, somewhat like the "dromedary" type of poliomyelitis. The fever was usually slight in the milder cases and was accompanied by dizziness, irritability, ataxia and personality changes. In the more severe cases, the fever was higher and the symptoms more severe. Disorientation, aphasia, apathy and confusion were common. Very severe cases had hyperpyrexia, in a few cases as high as 108° F., and delirium, convulsions, stupor and coma. Most of the patients showed signs of nuchal rigidity with positive Kernig and Brudzinski signs. Paralysis of the extremities were not unusual, and retention of urine was frequently met with. Occasionally there was incontinence of urine or feces. A number of patients showed involvement of cranial nerves, particularly the facial. Changes in deep and superficial reflexes were noted; in some cases these were exaggerated, in others diminished or absent.

The Babinski sign was occasionally positive.

The clinical course was usually short, recovery occurring in 1 or 2 weeks, and being complete. Relapses were occasionally noted. What was striking to observe was that even patients with the most alarming symptoms at onset, such as hyperpyrexia, convulsions and coma showed remarkable improvement within a period of 72 hours, and then rapidly progressed to complete recovery. Most of the cases were able to leave the hospital within 2 weeks. Of the 41 that survived, 1 could not be located for follow-up, 38 made a complete recovery, 1 had residual hemiparesis and 1 residual optic neuritis half a year after onset.

Spinal fluid examinations were made at least once in all but 3 cases. Clear fluid under pressure was the commonest finding. In 16 cases the cell count was less than 10 per ml.; in the rest the count varied from 14 to several hundred with average of 100, lymphocytes predominating. The protein concentration was under 35 mg. per ml. in 10 cases and from 36 to 110 mg. per ml., with an average of 61 in 21 cases. It was not reported in the others. Sugar was normal in all. Cultures of the fluids were uniformly sterile.

Mortality. A high mortality is reported both in England and Holland. The Andrewes Committee<sup>18</sup> reported a fatality of 58% in England for the years 1922-1924. For the years 1927-1929 the Rolleston Committee<sup>7</sup> reported a fatality of 47%. In Holland the fatality was 31% for all cases reported up to 1929.<sup>4</sup> In Scotland, fatality rates differed in the same year for Glasgow<sup>1</sup> (29%) and Fife<sup>17</sup> (50%). The Office Internationale d'Hygiene Publique<sup>7</sup> reported 33% fatality for Germany, 26% for Austria, 53% for Norway and 25% for Sweden. In the United States, Armstrong<sup>3</sup> found

a fatality of 37% in the 71 cases collected by him for the 10 year period 1922-1932. In general, the mortality appears to vary from 30 to 50%. This, of course, is a crude fatality rate. Most of the deaths were not autopsied, and if our experience is a guide, some of the deaths may be due to other causes.

Although Comby<sup>6</sup> was probably the first to report a case of encephalitis following vaccination, Lucksch,<sup>13</sup> in 1924, first called attention to the pathology of the disease. However, he confused it with epidemic encephalitis. Two years later, Turnbull and McIntosh<sup>22</sup> published a careful histologic study of 7 cases for the Committee on Vaccination. Similar studies were reported later by Perdrau,<sup>15</sup> Wilson and Ford<sup>25</sup> Gordon<sup>8</sup> and others. Grossly, there is little to distinguish the brain and cord of a case of postvaccinal encephalitis from that of other types of encephalitis. Histologically, however, there are great differences. The meningitis is of a mild character. The distinctive lesions are in the brain and spinal cord with areas of softening in which demyelination can be demonstrated. White and gray matter are both involved. In virus encephalitis, cuffing, and infiltration of the Virchow-Robins space frequently occur, but in postvaccinal encephalitis, in addition to the cuffing, areas of softening occur which extend some distance beyond the vessels and demyelination can be demonstrated in them. They are not associated with vascular thrombi. The same lesions appear in encephalitis following smallpox, chickenpox and anti-rabic vaccination, and are similar to those found in disseminated sclerosis.

The 4 deaths that occurred in the group of 45 cases here reported showed no such lesions at post mortem. In 2 cases the only lesions were marked congestion of the brain.<sup>9</sup> In the other 2, cuffing of the vessels in the brain and

\* Sections of one of these cases were examined by Dr. P. Sacerdote, pathologist of the Mt. Vernon Hospital, and in the Division of Laboratories and Research of the N. Y. State Health Department. Sections of the other case were furnished by Dr. Chester Brown, pathologist of Lincoln Hospital, and were kindly examined for us by Dr. Thomas M. Rivers of the Hospital of the Rockefeller Institute.

cord was demonstrated, but it did not extend beyond the Virchow-Robins space, and no demyelination was present.<sup>†</sup>

Whether deaths may occur in postvaccinal encephalitis without the occurrence of typical lesions it is difficult to state. Dr. Rivers says that although he supposes that it could happen, he would be loath to make a diagnosis of post-infectious encephalitis unless a characteristic picture were present, since in frank cases of postvaccinal encephalitis that die very early after the appearance of symptoms and signs, demyelination is usually present.<sup>16</sup> Although we have ascribed the 4 deaths in our series to postvaccinal encephalitis, definite proof on the basis of accepted pathological changes is lacking.

**Etiology.** Attempts to recover virus from the brains of 3 cases that were autopsied were unsuccessful. Herzberg-Kremmer and Herzberg<sup>10</sup> recovered vaccinia virus from the blood of 8 out of 17 vaccinated persons from the third to the tenth day after vaccination. They recovered virus from the tonsils of 2 cases on the 12th and 15th day, and quote Gins who recovered virus from the tonsils 3 to 6 days after vaccination. They also found virus in the spinal fluid and in the pharyngeal secretions of a case of postvaccinal encephalitis on the 12th day after vaccination. Ohtawara<sup>14</sup> recovered vaccine virus from the blood of his own child on the 7th day after vaccination. Blaxall<sup>18</sup> obtained vaccine virus from the brains of 3 fatal cases, and Turnbull and McIntosh<sup>22</sup> from 2 fatal cases. Blaxall<sup>18</sup> states that vaccine virus was found in the brains, liver and blood of calves which had been vaccinated, up to the

13th day, in rabbits up to the 10th day and in monkeys up to the 8th day. According to Ohtawara<sup>14</sup> vaccine virus enters the blood stream on the day after vaccination and is recovered in rabbits up to the 10th day.

It is obvious, from the reports quoted, that vaccine virus regularly enters the blood stream soon after vaccination; its presence in the brain in cases of postvaccinal encephalitis is therefore no proof that the virus is responsible for the pathological changes. A number of investigators have been unable to reproduce lesions of postvaccinal encephalitis in animals by injection of vaccine virus, although others have been successful.<sup>23</sup> Many theories have been offered to explain the etiology of the disease, but none has been proved.

**Treatment.** No specific therapy was used in any of our patients. Recovery appears to be complete in most cases, wherever they occur, irrespective of the therapy used. Treatment with convalescent serum was suggested by the Rolleston Committee and has been advised by several authors, but no one has used it in a series of cases with adequate controls to make significant an expression of opinion of its value.

**Summary.** 1. Forty-five cases of encephalitis occurred in New York City in 1947 following the vaccination of about 5,000,000 people, a case incidence of approximately 1 to 110,000 vaccinations.

2. There were 4 deaths. However, none of them showed post mortem lesions in the brain characteristic of postvaccinal encephalitis.

3. The age distribution, pathology and etiology of the disease are discussed.

<sup>†</sup> We are indebted to Dr. R. Aronoff, pathologist of Greenpoint Hospital, and to Dr. Thomas Gonzalez, Chief Medical Examiner, for putting at our disposal tissues from brain and cord, and to Dr. Thomas M. Rivers for examining the histologic sections.

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# PROGRESS OF MEDICAL SCIENCE

## RADIOLOGY

UNDER THE CHARGE OF  
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AND

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## ROENTGENOLOGIC MANIFESTATIONS OF SCLERODERMA

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SCLERODERMA is a systemic disease which affects not only the skin and subcutaneous tissues but many internal organs. The exact extent of the visceral involvement is not known, but it is a well-established fact that the gastro-intestinal tract, the lungs, the heart and the kidneys are affected at times. It seems probable that further studies will reveal that the connective tissue of almost any part or organ of the body will at times show evidence of involvement by scleroderma. The widespread character of this disease is shown by the fact that even the periodontal membrane of the teeth is involved in many cases. Only in recent years have postmortem examinations given detailed descriptions of the pathologic findings in patients with scleroderma who have died. Greater familiarity with the various pathologic manifestations of scleroderma will certainly lead to a better understanding of the extent and character of this disease. The recent interest in the visceral involvement by scleroderma has been stimulated to a considerable extent by the roentgenologic evidence that cer-

tain internal organs have been affected.

There are 3 types of scleroderma: diffuse scleroderma, acrosclerosis and circumscribed scleroderma (morphea). This review is concerned only with the first 2 types. Acrosclerosis is a combination of Raynaud's phenomenon and scleroderma which starts almost invariably in the extremities and later involves the face and neck. In most instances the Raynaud's phenomenon precedes the cutaneous sclerosis. Diffuse scleroderma develops insidiously as a rule and may begin about the extremities, the neck, face or trunk. In most instances this type is not accompanied by Raynaud's phenomenon. The progression of the disease is usually more rapid in diffuse scleroderma than in acrosclerosis, and the prognosis is considered worse in diffuse scleroderma. Visceral involvement is seen most frequently in acrosclerosis, although it is reported occasionally in patients who have diffuse scleroderma.

The fundamental disturbance in scleroderma seems to be an abnormal change in the collagen. At first there is edema of the connective tissue and

infiltration by lymphocytes and mononuclear leukocytes. As the lesions progress, the edema and cellular infiltration disappear, and the disturbance of the colloidal collagen predominates. The collagen fibers become enormously thickened, and new ones are formed. Along with this there are degeneration and fragmentation of the elastic fibers and of the muscle. This proliferation and alteration of the collagen fibers accounts for the induration of the tissue. Raynaud's phenomenon often accompanies atherosclerosis. There may be a direct relationship between the two conditions, but since the pathogenesis of neither is well understood, the significance of this association cannot be appraised as yet. Vascular lesions, principally marked intimal thickening, are sometimes seen in organs affected by scleroderma, but this is not a consistent finding and there is good evidence to indicate that the lesions of scleroderma are not secondary to the changes in the arteries. This will be discussed later when the pathologic changes seen in the gastro-intestinal tract, the heart and the lungs are described.

**Gastro-intestinal Tract. Esophagus.** Ehrmann,<sup>6</sup> in 1903, was the first to detect visceral involvement by scleroderma. This was observed in a patient who had scleroderma and in whom dysphagia developed. When esophagoscopy was performed, it was noted that there were changes in the wall of the esophagus. In 1931, Rake<sup>20</sup> reported a case of scleroderma in which there was roentgenologic evidence of involvement of the esophagus, along with other visceral manifestations that will be described later. Constriction of the lower part of the esophagus had been observed roentgenologically. At necropsy there was dilatation of the esophagus without any narrowing of the esophagogastric juncture being found. The mucosa of the lower three fifths of the esophagus was lacking.

Since this description was given by Rake, various observers have noted roentgenologic evidence of esophageal involvement by scleroderma. In many instances the cases are merely reported as showing constriction of the lower part of the esophagus with perhaps some dilatation. Fessler and Pohl<sup>7</sup>, Kuré<sup>13</sup> and his associates, and Weissenbach<sup>23</sup> and his associates gave more complete descriptions of the roentgenologic manifestations of scleroderma of the esophagus. They observed that there was a diffuse dilatation of the esophagus and that the barium mixture was carried through the esophagus very slowly, especially when the patient was recumbent. They further noted that there was absence of the normal peristaltic movements, that there was gaping of the esophagus and that there was a tendency for the barium to adhere to the walls of the esophagus. Weissenbach and his associates and Fessler and Pohl also described constriction at the lower end of the esophagus.

In 1944 Hale and Schatzki<sup>11</sup> gave an excellent description of the roentgenologic appearance of the gastro-intestinal tract in scleroderma. They reported not only on the changes seen in the esophagus but also on those seen in the stomach, small intestine and colon. Of 22 patients who had scleroderma, 7 had dysphagia and 5 of these showed roentgenologic evidence of esophageal changes. Of those without symptoms, 8 also showed esophageal changes suggestive of scleroderma. The extent of involvement of the skin had no correlation with the extent of the esophageal changes. The changes that Hale and Schatzki observed in their cases in which scleroderma of the esophagus was present were as follows:

1. The time of transit of the barium mixture through the esophagus was prolonged.

2. In some cases, the lower part of the esophagus seemed narrow and gave

the impression of resisting dilatation, although the walls did not seem rigid. Above the narrow segment the esophagus seemed somewhat dilated.

3. There was a tendency for the esophagus to stay open after the bolus of barium had passed, and the esophagus then seemed to contain air. Barium had a tendency to remain adherent to the wall of the esophagus.

4. There was loss of peristalsis, and gravity was the force which emptied the esophagus. This, of course, became obvious only when the patient was in the horizontal position.

5. There was sometimes a slight resemblance to cardiospasm, but there never was complete obstruction such as occurs in cardiospasm. Also the narrowing was not limited to the esophago-gastric juncture but affected the lower one half or one third of the esophagus. There was never great dilatation such as is seen frequently in cardiospasm.

Lindsay, Templeton and Rothman<sup>14</sup> observed 5 cases with esophageal changes, and their findings were similar to those of Hale and Schatzki<sup>11</sup>. Three of their patients had strictures of the esophageal ampulla. All had disturbances of peristalsis. In 4 cases the primary peristaltic wave disappeared at the level of the suprasternal notch. In the other case the primary wave continued but was too weak to propel the bolus of barium. The esophagus did not contract after the wave but distended immediately, so that the barium regurgitated upward past the wave. Air remained in the esophagus when the patient was in the horizontal position, and when the patient sat up the esophageal walls did not collapse normally. Continued swallowing of barium while the patient was in the recumbent position would cause the barium mixture to be pushed into the stomach; otherwise the barium would merely remain pooled in the esophagus for a prolonged period. When the patients were

lying down or in the Trendelenburg position, the barium mixture would flow into the upper part of the esophagus, behavior which is abnormal.

Olsen, O'Leary and Kirklin<sup>18</sup> reported 15 cases in which there was roentgenologic evidence of involvement of the esophagus by scleroderma. In 6 cases there was esophageal dilatation with atony of the esophageal musculature. Peristalsis was decreased or absent. In 4 cases there was some obstruction at the esophago-gastric juncture. In 9 cases esophageal hiatal hernias were seen. In 2 cases of this group there was also esophageal dilatation resembling cardiospasm. In 6 of the cases with diaphragmatic hernia, the hernia was of the short esophagus type with narrowing of the lower part of the esophagus and stricture at the esophago-gastric juncture. Olsen and his associates have given their concept of the manner in which scleroderma affects the esophagus and the way in which it progresses, and this seems most logical. When scleroderma affects the esophagus, the latter becomes stiff and indurated and loses normal peristaltic movement. In early cases there will be seen some lagging of barium mixture at the esophago-gastric juncture because the peristalsis is not sufficiently strong to inhibit the cardiac sphincter as it normally does. As the esophagus becomes stiffer, it remains gaping and does not collapse when empty. Ultimately this leads to a patulous esophago-gastric juncture, and gastric secretions may then flow from the stomach into the lower part of the esophagus, especially when the patient is recumbent. This, of course, leads to marked inflammation of the lower part of the esophagus. This portion of the esophagus becomes narrowed as the result of spasm and inflammatory cicatricial changes, and there is often a definite stricture at the lower end. The changes that affect the esophagus not only cause it to be narrowed but often may

cause it to be shortened. Thus esophageal hiatal hernias of the short esophagus type may be seen.

The esophagoscopic examination of patients who have scleroderma can be done only with considerable difficulty, but in some instances this has been done. By this method of examination, Ehrmann noted thickening of the esophageal wall, and Schwarz<sup>22</sup> found esophagitis. In 3 cases Lindsay and his associates observed that the wall of the lower half of the esophagus was diffusely reddened and apparently thickened, with a lessened tendency to form normal folds. In the lower third there was a diffuse layer of white exudate which could be easily separated, leaving a granulating base. In 1 case they saw a smooth scar-tissue constriction which would not allow the passage of the esophagoscope. There was superficial ulceration in the region of the stricture. In 2 other cases the fibrous constriction was not so dense and the mucosa showed no exudate or erosion below the constriction, but at the constriction there was exudation and superficial ulceration. These observers stated that they consider the mucosal changes to be the result of chronic inflammation due to retention and peptic esophagitis secondary to regurgitation. Goetz<sup>9</sup>, also, described the lower third of the esophagus as being red and bleeding easily. Olsen and his associates described the esophagoscopic findings in 8 cases. In 5 of these they found esophageal hiatal hernias. Two of these had strictures at the esophago-gastric juncture, and the esophagus was abnormally short. Two others with diaphragmatic hernia were seen to have ulceration at the esophago-gastric juncture. Of those without diaphragmatic hernia, 1 had severe atrophic esophagitis and the esophagus was dilated without any stricture being apparent. Another showed severe induration and thickening of the esophageal wall. One other case showed minimal changes.

the mucosa being pale and smooth but otherwise normal.

The pathologic changes in the esophagus that have been seen at necropsy have varied considerably, as one would expect. Rake<sup>20</sup> found dilatation of the esophagus, chronic ulcerative esophagitis being present. The mucosa of the lower three fifths of the esophagus was lacking. No constriction was present at the lower end of the esophagus. Auerbach's plexus appeared normal. Dowling<sup>21</sup> reported a case in which there appeared to be obstruction at the juncture of the middle and the lower third of the esophagus, but this was not confirmed at postmortem examination. Bevans<sup>1</sup> found that in 1 of her 2 cases the esophageal mucosa was replaced by fibrinoid material, the submucosa was sclerotic, and the muscular layers were atrophic and extremely fibrosed. Goetz also found extensive pathologic changes in the esophagus, including erosion of the mucosa, thickened submucosa, hypertrophy of the muscularis mucosae and atrophy of the muscular coats. There was leukoplakia of the lower part of the esophagus with some calcification in the connective tissue in 1 case. Goetz described changes in the myenteric plexus which led him to postulate that spasm may be the initial process and that neuro-muscular dysfunction leads to secondary ulceration.

Many of the changes in the esophagus that have been described by various observers are undoubtedly the result of chronic inflammation, and it is difficult in many instances to distinguish the alterations due to infection from those caused primarily by scleroderma. It seems only too likely that minimal changes due to scleroderma itself may be completely obscured by chronic infection. It may also be true that early pathologic manifestations of scleroderma, such as edema of the tissues, would be considerably altered by the fixation of this tissue and would not be recognized or would be consid-

ered within normal limits by the pathologist. It might also be that a slight increase of collagen fibers would not be very conspicuous and would be taken by the general pathologist to be within the limits of normal. Abnormality in the myenteric plexus has not been a very constant finding in the cases reported; it seems to me that a neuromuscular disturbance with associated spasm is not a probable initial phase of scleroderma of the esophagus. It seems likely that the earliest pathologic changes that occur may be earlier recognized when they cause disturbance of function which can be seen roentgenologically, then when searched after by means of the microscope after the tissue has been fixed. Certainly at times scleroderma must be difficult to identify by pathologists, since visceral scleroderma was detected only relatively recently.

Scleroderma of the stomach, small intestine and colon has been reported much less frequently than esophageal involvement. Rake in 1931 observed a case in which not only was the esophagus affected but in which he observed roentgenologic evidence of obstruction at the pylorus and dilatation of the small and large bowel. Schatzki<sup>21</sup>, and Hale and Schatzki found the following alterations in the gastro-intestinal tract below the esophagus as seen by roentgenologic observations:

*Stomach.* Delayed emptying may be of considerable duration. This is difficult to judge in comparison with the normal.

*Small Intestine.* 1. There was widening of the small bowel, especially the upper part, including the duodenum. This extended to the ileum in only 1 case.

2. Marked delay of the passage of barium through the small bowel was conspicuous.

3. In 2 cases a peculiar sacculaton along the mesenteric border of the

small intestine was noted and in 1 case this was confirmed at operation.

*Colon.* Multiple short segments of localized narrowing were seen throughout the colon. There was sacculaton of the bowel between the affected segments.

Bevans reported roentgenologic evidence of obstruction and disturbance in the mucosal pattern in the small intestine. Examination of the colon indicated irregular muscular contraction and diffuse dilatation. Goetz, and Goetz and Cole-Rous<sup>10</sup> have given a detailed description of the roentgenologic manifestations of scleroderma of the stomach and intestines. The stomach may be atonic and retain barium for a long period. The most striking change was the paralysis or lack of peristalsis particularly affecting the duodenum and the jejunum. There was localized dilatation of loops of small intestine, and the barium column broke up into segments. There was marked retention in the duodenum. The small intestine was, at times, found to be generally dilated, suggesting paralytic ileus. The colon showed narrowing, rigidity and sacculaton. Pugh, Kvale and Margulies<sup>19</sup> found peristalsis in the small intestine to be definitely sluggish, and segments were seen to remain without normal contractibility for a considerable period before ineffective peristalsis would begin again. The relative lack of contractibility was seen not only in the duodenum but also in the terminal portion of the ileum.

Rake described the pathologic changes in his case as consisting of dilatation of both the large and the small intestine without any evident hypertrophy. There was no mechanical obstruction to account for the dilatation. Bevans noted markedly increased fibrosis, atrophy of the musculature, vascular lesions and edema of the intestines. In Goetz's cases the following pathologic changes were observed: (1) marked atrophy of the intestinal wall;

(2) fibrous replacement of muscle fibers with occasional lymphocytic and plasma-cell infiltration; (3) prominence of the neuromuscular apparatus. The latter change was accompanied by a conspicuous lack of ganglion cells and fibrosis in some cases. Goetz's description is very complete and warrants careful study by those interested in this subject. Schatzki described the pathologic findings in a segment of resected small intestine which appeared to be affected. There was only slight thickening of the intestinal wall with edema and hypertrophy of the submucosa and of the interstitial tissue of the mesentery. Later, at necropsy, no characteristic histopathologic changes were found in the abdominal viscera.

*Lungs.* In 1941 Murphy, Krainin and Gerson<sup>17</sup> first described the roentgenologic manifestations of scleroderma of the lungs. In this case they noted that "within both pulmonary fields, exclusive of the apices and the lateral aspect of the bases, there was a diffuse network-like shadow extending from the cardiac border to the periphery. This shadow was dense in the lower halves of the lung fields but thinned out and became strandlike in the subclavicular regions." Bronchograms were negative. Since the report of Murphy and his associates, there have been other observers who have found definite roentgenologic evidences of pulmonary scleroderma. In the same year, Linenthal and Talkov<sup>18</sup> reported 3 cases of Raynaud's phenomenon with pulmonary fibrosis. In each of these cases atherosclerosis was present. In the cases of scleroderma of the heart reported by Weiss and his associates there was increased pulmonary fibrosis, especially in the base, and this was confirmed at necropsy. Abnormal pulmonary changes were observed by Goetz, there being relative density in the bases and apical emphysema.

In reporting a case of scleroderma with visceral involvement, Pugh, Kvale

and Margulies made the following observations: "The pulmonary involvement by scleroderma, as shown by the roentgenogram, manifests itself as diffuse pulmonary fibrosis which is usually more conspicuous in the lower portions of the lung. The roentgenologic manifestations of many pulmonary diseases can be described only with difficulty. This is especially true with regard to various types of pulmonary fibrosis. The pulmonary lesions of scleroderma seem to have a rather distinctive roentgenographic appearance but this defies adequate description." This opinion was based, not only on the 1 case reported, but also on several other cases with pulmonary involvement that had been seen. After seeing several additional cases since then, I am more convinced than ever that in many cases the roentgenologic diagnosis of pulmonary scleroderma can be made without knowledge of clinical data.

Notthafft, Matsui and Kraus are quoted by Murphy<sup>17</sup> and his associates as having found pulmonary changes at necropsy in patients who had died of scleroderma. Weiss and his associates demonstrated increased fibrosis of the lungs at necropsy. This increase was in collagen fibers. In 1 of their 2 cases in which necropsy was performed there was marked intimal thickening of the pulmonary arteries, but the other case did not show this change. Thickened alveolar septa and vascular lesions were found in the lungs by Goetz. Pulmonary fibrosis, which was mostly peribronchial and perivascular and which was accompanied by marked vascular changes, was the finding in Bevans' cases. The most thorough study of the pulmonary changes in scleroderma has been made by Getzowa.<sup>19</sup> Her description was in great detail, and it is not possible to give, at this time, an adequate résumé of her findings. Briefly it may be stated that she found that the alveolar walls contained collagen

fibers, which replaced the elastic tissue that is normally present. In some places, especially at the periphery, the alveolar walls disintegrated to a considerable extent, and there resulted an emphysematous or cystic-appearing condition. These cystic regions were sometimes large enough to compress the adjacent lung tissue. The cysts were usually epithelized. In other regions, especially the bases, the fibrosis led, not to cystic changes, but to compression and obliteration of the alveoli. Dostrovsky<sup>2</sup> examined 3 cases with pulmonary fibrosis, in 2 of which necropsy was performed. His pathologist reported that in the lungs there was alveolar distention, occasionally assuming cystic dimensions in the cortical and subcortical regions of the upper portions of the lungs, with atelectasis at the bases.

**Heart.** Scleroderma of the heart was not recognized until 1943, when Weiss<sup>24</sup> and his associates studied 9 patients with generalized scleroderma who had symptoms and signs of heart disease. The roentgenologic findings in these cases were in no way diagnostic of scleroderma but were suggestive. All of the patients had cardiac enlargement, varying from moderate to a marked degree. The cardiac silhouette was triangular. In most cases the heart beat was of poor amplitude as was shown by roentgenoscopic examination. There was nothing roentgenologically to suggest hypertensive or valvular heart disease. Calcification of the valves could not be detected. The left ventricle was not predominantly enlarged, and the left atrium was not unduly prominent. Weiss and his associates stated that the triangular cardiac contour and the weak pulsation of the heart somewhat suggested myxedema heart or pericardial effusion.

The electrocardiograms in the 8 cases so examined showed auricular fibrillation (1); premature ventricular beats (3); partial heart block (2); intra-

ventricular block and later bundle-branch block (1); left axis deviation, otherwise within normal limits (2), and abnormally low electromotive force (3).

Weiss and his associates described the pathologic changes found in the hearts of 2 of the patients who died. In both cases there were unusual regions of fibrosis in the myocardium. These scars had certain resemblances to those due to vascular changes but were unlike such vascular lesions in the following ways: (1) the lesions in the myocardium in the patients who had scleroderma were not in any particular relation to arteries, these structures being indifferently included in the scars or not; (2) the vessels were normal or showed minor intimal thickening without thrombosis or significant diminution of the caliber of the lumen; (3) the deposits of hemosiderin often seen in regions of myocardial scarring due to vascular lesions were entirely absent; (4) within the scars the myocardial fibers were preserved in small numbers even in the center of the lesions. This was true also of fat cells and blood vessels. Weiss and his associates stated that in their opinion the lesions consisted of a primary overgrowth of fibrous tissue with secondary destruction of other myocardial structures.

On reviewing Rake's case, I find that he observed scars in the myocardium but made no further mention of it. Without much doubt his patient had scleroderma of the heart.

Goetz has also found patients with scleroderma of the heart. Cardiac involvement was diagnosed on the basis of kymographic examinations which showed marked blunting of cardiac excursions. In 1 case hardly any excursions were noted. In most cases the heart was small and the contour was normal. The blunting was found in 4 cases, and in 3 cases in which necropsy was performed the lesions were found.



One patient with cardiac lesions had a normal electrocardiogram. In other cases the electrocardiogram was abnormal, ranging from bundle-branch block to auricular fibrillation. In 1 patient all heart beats were extrasystoles, which originated from 8 different foci. Goetz found pathologic changes in the hearts of 3 patients which were identical with those described by Weiss and his associates. He stated that dyspnea, cyanosis and orthopnea, which occur in patients with scleroderma, may be due to (1) vascular changes in the lungs, (2) thickened alveolar septa, (3) emphysema, (4) rigidity of the thorax, or (5) myocardial fibrosis.

Bevans found myocardial changes similar to those described by Weiss and his associates. She also described vascular lesions involving especially the medium-sized and small-sized arteries of the myocardium.

Pugh, Kvale and Margulies reported a case with extensive visceral scleroderma in which dyspnea and electrocardiographic changes suggestive of scleroderma were present. There were an abnormally low electromotive force and left axis deviation. Mathisen and Palmer<sup>16</sup> have reported the finding of typical pathologic changes in the heart of a patient with scleroderma who died.

The pathologic changes found in the heart seem to be quite consistent in character. The nature of the cardiac lesions as described by Weiss and his associates, Goetz and Bevans seems to suggest very strongly that visceral involvement by scleroderma is primarily a condition in which there is proliferation of the collagen fibers, and it is not likely that this proliferation of fibrous tissue is secondary to vascular changes or to some disturbance of the autonomic nervous system.

**Dental Findings.** In 1944 Stafne and Austin<sup>23</sup> reported dental roentgenographic findings which are peculiar to patients with scleroderma. This consists of an increase in the width of the

periodontal space. Not all of the teeth may be affected, and the posterior teeth are involved more frequently than the anterior teeth. On the involved teeth the space which has been created surrounds the entire root of the tooth and is almost uniform in width. The uniformity of the width of the periodontal space as it is seen in scleroderma can be distinguished from that due to acute pericemental inflammation, pyorrhea alveolaris or traumatic occlusion, since in these latter conditions there is no such uniformity. The roentgenographic appearance in scleroderma is similar to that of teeth rapidly extruding from their alveolar sockets, but on clinical examination it will be found that the teeth are not extruded, for on closure these teeth are observed to be on the same plane of occlusion as the teeth which are not involved. The teeth are surprisingly firm in their sockets. In 1 case, 2 teeth were extracted and it was found that the periodontal membrane was from two to four times as thick as the normal. The arrangement of the collagen fibers of the periodontal membrane was definitely abnormal. The walls of the blood vessels in the periodontal membrane were thickened. A review of the dental roentgenograms of 127 patients with scleroderma revealed that 9 (7%) of the patients had the characteristic findings. A tentative diagnosis of scleroderma was made in 4 cases entirely on the basis of the dental roentgenographic findings and without knowledge of clinical data; in each instance the diagnosis was confirmed clinically.

**Absorption of Phalanges and Calcification.** For many years it has been known that in far-advanced cases of scleroderma, especially in the acrosclerotic type, there is absorption of the distal phalanges. It is not known just why this occurs. It may be the result of circulatory disturbance due to Raynaud's phenomenon, or it may result from the constricting effect of the

cutaneous sclerosis. Accompanying this there is at times an increased density of the bone of the phalanges. Synostosis between the distal and the middle phalanges may be seen. Calcinosis is found fairly frequently and often accompanies the absorption of the distal phalanges. The calcific deposits vary in size from minute sandlike particles to large plaques. Most frequently the deposits of calcium are seen in parts of the body subject to pressure, such as the finger tips, elbows and ischial tuberosities.<sup>4,5,12</sup> There may be hard plaques of calcium that can be palpated, and fairly frequently there is ulceration over the calcific deposits. As a rule calcinosis is seen only where there is cutaneous sclerosis, but rarely it has been seen where the overlying skin is normal. The exact cause for calcinosis in these cases is not known, but it is probable that it results from abnormal tissue metabolism. Durham<sup>4</sup> and Jackman<sup>12</sup> have suggested that in scleroderma the devitalized tissues have an abnormally low carbon dioxide tension with a resulting trend toward alkalinity and that this leads to precipitation of calcium.

**Generalized Involvement.** There have been some reports of very extensive cutaneous and visceral involvement

with scleroderma. In Rake's case there were absorption of the distal phalanges, involvement of the entire gastro-intestinal tract and probable involvement of the lungs and heart. Hale and Schatzki described the changes as seen affecting all the gastro-intestinal tract. Weiss and his associates reported cases with scleroderma of the heart in which there was also esophageal and pulmonary involvement. Goetz reported in detail on a patient who had calcinosis, erosion of the distal phalanges and involvement of the entire alimentary tract, heart and lungs, and he had other patients similarly affected. Pugh and his associates described a case with roentgenologic manifestations of scleroderma affecting the lungs and the entire gastro-intestinal tract and with probable cardiac involvement.

**Conclusions.** In patients with scleroderma, especially the type called acrosclerosis, visceral involvement occurs fairly frequently. The roentgenologic diagnosis of such involvement has been made and has been confirmed by pathologic findings. The possibility of visceral involvement should be suspected in cases with scleroderma, and roentgenologic investigations should be carried out.

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# THERAPEUTICS

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## TREATMENT OF THE LEUKEMIAS

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THE problem of the leukemias is one of the most challenging in the field of medicine. Considerable advance has been made in diagnostic techniques which allows the positive recognition of these diseases, and this undoubtedly is a factor in the apparent increase in their occurrence.<sup>74</sup> However, knowledge of the fundamental pathologic physiology concerned is relatively meager. There is now a voluminous literature on the study of leukemia in mice, which animals may be inbred to perpetuate strains with a very high natural incidence of the disease. The results of this experimental work have increased our knowledge of important aspects of leukemia, especially in regard to the effectiveness of therapeutic agents. Because it is the consensus that the leukemias of mouse and man are similar,<sup>25</sup> the results of these experiments serve as guides to the study of the treatment of humans. A résumé of the effectiveness of therapeutic agents against mouse and human leukemia was published by Flory in 1944.<sup>21</sup>

The therapeutic agents used in human leukemia are, at most, palliative in their effect, and it cannot be stated with certainty that the use of any one

of them prolongs the life of the patient. That the patient may be made more comfortable by treatment, however, cannot be denied, and at present one must be satisfied if this can be accomplished. Before attempting to evaluate the effectiveness of some of the agents in present use it will not be amiss to remark on the natural course of the disease as we know it. Because leukemia, acute or chronic, not uncommonly undergoes spontaneous remissions it is dangerous to conclude from a small series of cases that the agent used is responsible for any improvement. This is particularly true if the patients are followed for only a short period after the therapeutic trial. A timely reminder of the frequency of spontaneous remissions and of the caution required in the evaluation of therapeutic results in acute leukemia has recently appeared.<sup>13</sup> It should be mentioned that occasionally patients with chronic myelogenous leukemia may live 10 years, and rarely longer, although the average life span is a little over 3 years. More important, however, is it to recognize the relatively "benign" course that chronic lymphogenous leukemia not infrequently pursues in older

patients. In these fortunate ones there are usually no signs or marked symptoms of the disease, and there is usually no anemia. The white blood count, however, varies usually between 30,000 and 100,000 per mm.<sup>3</sup> with a high (60% to 80%) lymphocyte count. This situation may exist for years without treatment. Because the age of patients is often not given in a report, the true effectiveness of a therapeutic agent may be masked by the inclusion of an unknown number of older patients whose disease may progress relatively slowly. The report of Hamann<sup>31</sup> comments on precisely this point. Eight of her 51 patients with chronic lymphogenous leukemia treated with external irradiation lived more than 5 years; of these, 7 were above the age of 50 at the time of onset of their disease. This is important to know in evaluating the effect of the treatment on longevity. Another variable which often makes it difficult to compare the relative effectiveness of 2 forms of treatment is the length of time from the onset of the disease to the institution of therapy. From even a brief consideration of the natural variability of these diseases it becomes evident that only a statistical analysis of relatively large numbers of patients with attention to the factors noted above can give any suggestion as to the effectiveness of any therapy on longevity. It is not uncommon to see treatment improve the patient's blood count and symptoms, but have little apparent effect on the course of the disease.

A few generalizations concerning therapy may be mentioned before considering the various treatments in detail. In the chronic forms of myelogenous and lymphogenous leukemia the appearance of signs and symptoms of anemia, hemorrhagic manifestations, evidence of a very high basal metabolic rate (hyperpyrexia, weight loss) or pressure effects from an enlarged spleen

or from enlarged lymph nodes are indications for treatment. The level of the white blood cell count *per se* is not a guide, for not infrequently one sees a patient who is entirely comfortable despite a marked elevation of the leukocytes. In evaluating treatment it is well to remember that the appearance of enlarged lymph nodes in a patient with chronic myelogenous leukemia, and the appearance of a marked anemia in a patient with chronic lymphogenous leukemia both are of grave prognostic significance. The duration of life after the appearance of these signs is usually only a few months, regardless of therapy. Chemotherapeutic agents are of importance and are used, despite the fact that radiation is of proven benefit, because of the well known eventual development of radio-resistance. It is thought by many that the best results may be obtained by a combination of chemotherapy with radiation therapy, for evidence is accumulating that radio-resistance may be influenced by one or more courses of some of the chemical agents.

**Chemotherapy. ARSENIC.** According to Forkner,<sup>23</sup> potassium arsenite enjoys the reputation of being the oldest form of treatment for leukemia. It was used fairly widely about the turn of this century, but then was neglected until its revival by Forkner and Scott in 1931.<sup>24</sup> The mode of action of this chemical is poorly understood. Piney<sup>68</sup> states that it acts by decreasing the reproductive activity of myeloblasts. Warren<sup>82</sup> studied the effects of potassium arsenite on normal rabbit marrow, normal human marrow, and on human leukemic leukocytes by the use of the Warburg apparatus and found that respiration of the cells was depressed by this chemical. This was accompanied by an accumulation of lactic acid in these tissues. This agent has been found to be effective against several strains of mouse myelogenous leukemia<sup>21</sup> and, in a com-

parative study with urethane, benzol, and Roentgen-rays, was found to be the most efficient in lengthening the survival time in 3 transfer lines of this disease.<sup>44</sup> These same authors report that their 2 strains of mouse lymphogenous leukemia did not respond to the arsenite, and this has been the experience of Flory<sup>21</sup> in 3 out of 4 strains of this type. In another comparative study on mouse leukemia potassium arsenite was found to be the most effective of all the arsenicals tested.<sup>22</sup>

Radioactive arsenic has been used to study the distribution of potassium arsenite in tissues of the rabbit,<sup>12</sup> higher apes,<sup>53</sup> and man.<sup>38</sup> In rabbits, following the intravenous injection of subtoxic doses of "tagged" sodium arsenate, the distribution of the arsenic was found to be relatively non-uniform. The main storage sites were the muscles, bone, and skin, although the concentration in these tissues was relatively low. The cancellous bone was not noted to fix arsenic any more permanently than any other tissue. The concentration in the spleen, bone marrow, and walls of the stomach and intestine reached fairly high levels, but for brief durations. From the study in apes it was demonstrated that there is little evidence for the replacement of phosphorus by arsenic in the tissues. In man, arsenic was found to be widely distributed after injection, with the largest total amount in the skeletal muscles. There was no evidence that arsenic accumulated in rapidly growing tissues. In the blood, the leukocytes (type?) contained about 10 times the amount of arsenic as did the erythrocytes. None of these experiments supplies a direct explanation of the clinical effectiveness of arsenic.

In humans, potassium arsenite is most effective in chronic myelogenous leukemia, occasionally effective in chronic lymphogenous leukemia, and only very rarely of use in the acute form of the disease, where it may re-

duce the level of the circulating leukocytes. When this drug is given according to the schedule of Forkner, it is common to note marked hematologic and clinical improvement in patients with chronic myelogenous leukemia. The leukocyte count may return to normal with a marked decrease in the number of immature cells. The red cell count commonly rises, the splenomegaly decreases, and the patient may appear clinically well. No toxic effect on the platelets has been reported, and there is no contra-indication to its use in the leukopenic stage of the disease. The initial dose is 3 minims in orange juice or milk given 3 times daily after meals. After 2 days this dose is increased by 1 minim daily (*not* 1 minim t.i.d.) until one of two effects is attained: either the white cell count has fallen to between 10,000 and 20,000 per mm.<sup>3</sup> or intractable vomiting requires cessation of the medication. When the white blood count has fallen to this range, the medication is stopped for 4 days, then it is resumed at the same level, with a daily decrease in dosage of 1 minim. By watching the white cell count a maintenance dose is determined, and this is continued until toxic signs of the drug appear. Minor toxic effects are on the gastro-intestinal tract resulting in nausea, vomiting, and diarrhea. More serious are signs of renal irritation, dermatitis, and neuritis. The drug eventually has to be stopped in all cases, and this is usually because of its effect on the skin. The development of peripheral neuritis or exfoliative dermatitis constitutes an absolute contra-indication to further treatment. It is not unusual to maintain a patient in satisfactory remission for from 3 to 18 months with this drug. Although patients with chronic lymphogenous leukemia commonly are not benefited by potassium arsenite, Falconer<sup>65</sup> quotes a personal experience in such a case where the white cell count fell from 1,000,000 to

7,000 in 3 weeks of therapy. He is of the opinion, after reviewing his results in 39 cases of chronic myelogenous leukemia and 26 cases of chronic lymphogenous leukemia, that there is advantage in combining arsenic and Roentgen-ray therapy. Piney<sup>68</sup> agrees with this impression.

**URETHANE.** The first report concerning the effectiveness of ethyl carbamate on leukemia was by Paterson *et al.*<sup>67a</sup> in 1946, who used this agent following the demonstration by Haddow and Sexton<sup>29</sup> of its action on some animal tumors. Since then numerous investigators have published reports of its effectiveness in the leukemia of mice<sup>15,45,47a,47b,86</sup> and rats.<sup>63c</sup> In general it has been shown that survival time is lengthened, the white blood count is reduced (with a diminution in the number of immature cells), and that there is a reduction in the size of the lymph nodes and spleen when sub-anesthetic doses are given repeatedly. Several reports have appeared which indicate two of the toxic reactions encountered in experimental animals. It has been shown that prolonged administration of urethane increases the incidence of pulmonary adenoma in rats<sup>49</sup> and in mice.<sup>61</sup> Jaffe warns that this might occur in humans. In dogs the subcutaneous administration of the drug in doses higher than those given to patients produced a typical thrombocytopenic purpura.<sup>6</sup>

The mode of action of urethane is not understood, although it is thought to be effective through inhibition of mitosis of the leukemic cells.<sup>62,76</sup> These authors do not agree, however, on the changes which occur in the bone marrow pictures of treated patients. Craver<sup>1</sup> states he is unable to confirm the more marked effect of urethane on the less mature cells.

The dosage for humans is from 1.0 to 6.0 gm. daily, administered by mouth preferably in 0.5 gm. enteric

coated tablets to minimize nausea and vomiting. It may also be administered parenterally.<sup>7,36,75</sup> Bedinger, Poncher, and Limarzi<sup>1a</sup> have reported on its use in 17 patients with acute leukemia. Little or no benefit was derived except for a "rapid and marked fall in leukocyte count in all cases." This effect on the white cells has been observed frequently, but by no means invariably, in the author's experience; no beneficial effect on the course of the acute disease has been impressive. This is essentially the experience reported by Watkins *et al.*<sup>84</sup> Urethane is generally more effective in chronic myelogenous leukemia than in the chronic lymphogenous variety,<sup>67b</sup> but in each form may cause a reduction of leukocytes to normal with a decrease in the size of the spleen and lymph nodes.<sup>1,7,36,75</sup> Craver<sup>6b</sup> reports it to be productive of remission in only a fourth to a third of his cases. Piney,<sup>68</sup> on the other hand, thinks that urethane is preferable to benzol, more efficacious than arsenic, and is probably the most satisfactory treatment for chronic myelogenous leukemia. It is impossible at this time effectively to compare urethane with any other form of treatment because of the brief length of time that this drug has been used. Toxic reactions include anemia, agranulocytosis, and thrombocytopenia.<sup>7</sup> Two deaths have been reported, both presumably due to the drug.<sup>67a,85</sup>

**NITROGEN MUSTARDS.** This group of compounds, whose application has evolved from the discovery of their marked cytotoxic activity, has now been used rather widely in both animals and man. They have been found to prolong the life of mice with transmitted leukemia,<sup>5</sup> and have been used against Hodgkin's disease, the lymphomas, and the leukemias in man.

Of the many nitrogen mustards, the methyl-bis (beta-chloroethyl) amine hydrochloride (HN<sub>2</sub>) is the one most

widely used. The dosage schedule usually employed is 0.1 mg. per kg. body weight intravenously daily for 4 to 6 days. The drug may be given into the lumen of the tube of a rapidly running infusion in order to avoid its contact with the patient's subcutaneous tissue or skin. Because of the toxic action of these drugs on the hematopoietic system,<sup>43</sup> a complete blood count and platelet count should be performed daily during the course of treatment. If a marked depression of any of the blood elements occurs, the course should be interrupted. One of the most serious toxic effects, especially in leukemia patients who already have a depression of the platelets, is thrombocytopenia. The author has seen 2 patients die from cerebral hemorrhage which apparently resulted from severe vomiting associated with a profound platelet deficiency. Nausea and vomiting, often severe, are very common in from 1 to 3 hours following the administration of the drug. There is wide individual variation in this regard, however, for occasional patients have no such reaction.

In acute leukemia,  $\text{HN}_2$  has been reported to effect occasional and very brief clinical and hematologic remissions. Wintrobe *et al.*<sup>58</sup> report "fair" results in 3 of 8 cases of acute or subacute leukemia. They remark, however, that bone pain is often relieved in these patients, even by very small doses. Spurr *et al.*<sup>78</sup> found  $\text{HN}_2$  of little or no value in acute leukemia, but got promising results in some early cases of chronic lymphogenous leukemia. Others<sup>28</sup> indicate that in both forms of chronic leukemia, treatment often causes a reduction in the white cell count, a more normal differential picture, improvement in the bone marrow, and a more persistent beneficial effect from transfusions. Wilkinson and Fletcher<sup>87</sup> report on the use of the tris (beta-chloroethyl) amine in patients

with chronic leukemias, and indicate that it was usual to obtain a satisfactory fall in the total white cell count. It is generally agreed that the nitrogen mustards at present available are not superior to Roentgen-rays in the treatment of leukemia although occasionally they are useful in radio-resistant patients. One of the newer nitrogen mustards, SK 136, has been found to benefit chronic myelogenous leukemia about the same as  $\text{HN}_2$ , but usually does not cause nausea or vomiting. It gives "occasionally promising" results in acute leukemia but usually is "unsatisfactory."<sup>4</sup>

**BENZOL.** This drug has been used much more extensively in Europe than in America, where it has never been popular. The reasons for this reluctance to use it have been succinctly summarized by Watkins.<sup>83</sup> It is unsatisfactory because of the closeness of the therapeutic to the toxic dose, because of the great variations in susceptibility among different patients, and of the danger of producing aplastic anemia or granulocytopenia. That chronic exposure to benzol may be able to produce leukemia in man is suggested by Mallory *et al.*<sup>56</sup> and Hueper.<sup>37</sup> Kalapos,<sup>41</sup> on the other hand, concludes that benzol is a valuable drug in the treatment of leukemia, and states that in the dosage used (3 to 5 gm. daily) he has never noted toxic effects on the liver or kidneys. Forkner<sup>23</sup> was unable to find any evidence to support the contention that benzol was a useless or dangerous drug.

In mice, benzol has been noted to be effective in lengthening the survival time in 3 transfer lines of myelogenous leukemia.<sup>44</sup> It was found to be highly effective against a strain of mouse chloroleukemia, and to prolong the lives of mice with certain strains of lymphogenous leukemia.<sup>22</sup> Piney<sup>68</sup> has recently outlined the treatment course which he has found satisfactory. It is his belief that this drug is useful in chronic my-



elogenous leukemia and that dislike of it is ill-founded. It is probable that the therapeutic possibilities of this agent have not been sufficiently explored.

**Folic Acid, Folic Acid Derivatives, and Folic Acid Antagonists**—Heinle and Welch<sup>34</sup> have recently reported the results of their experience with pteroylglutamic acid in human leukemia. When this agent was administered to 3 patients with chronic myelogenous leukemia, a rapid hematologic and clinical relapse occurred in each case. In 2 patients with chronic lymphogenous leukemia no such relapse occurred under treatment. These investigators have also produced folic acid deficiency in 2 patients with chronic myelogenous leukemia by the administration of a diet low in folic acid, succinyl sulfathiazole, and a crude folic acid antagonist of which the active constituent was probably, but not certainly, methopterin.<sup>33</sup> In a period of 100 to 140 days on such a regimen there was a clear-cut clinical and hematologic remission. Administration of folic acid to 1 patient caused sudden and violent relapse with death. Substitution of a regular hospital diet for the low folic acid diet in the other patient caused a slower but eventually marked hematologic relapse necessitating treatment.

The effectiveness of teropterin or pteroyltriglutamic acid on tumor growth has been briefly reviewed by Karnofsky,<sup>42</sup> who concludes that there is no evidence that this substance has any influence on tumor growth in animals. Farber *et al.*<sup>18</sup> have administered teropterin and diopterin (pteroyldiglutamic acid) to a series of 90 patients with various neoplastic diseases. They found that the parenteral administration of these substances had no toxic or unpleasant effects, and that in some instances the tumors showed histologic changes attributable to therapy. Many of the patients experienced a sense of well-being. This same feeling of sub-

jective improvement is reported by Meyer<sup>58a</sup> to have occurred frequently in his series of patients with leukemia treated with teropterin in doses up to 200 mg. daily, but he was unable to determine any hematologic benefit in the cases of chronic leukemia. His patient with lymphoblastic leukemia seemed to show some reduction in the number of blasts with a corresponding increase in mature lymphocytes in both blood and bone marrow.

The action of folic acid antagonists in leukemia has been the subject of several studies. Meyer<sup>58a</sup> summarized his results with 2 folic acid antagonists in 5 cases of acute leukemia. In 3 of these there was a reduction in the total white count with a temporary shift to the right. More recently, Farber *et al.*<sup>19</sup> have reported on their experience with another folic acid antagonist—4 aminopteroylglutamic acid (aminopterin)—in the treatment of acute leukemia in children. Sixteen patients were studied, 10 of whom showed clinical, hematologic, and pathological evidences of improvement of 3 months' duration. They present the protocols of the 5 patients who experienced the best results, which deserve to be examined in detail by anyone interested in this report. They note stomatitis to be one of the toxic effects of this drug, but remark that it may produce even greater disturbances than they have encountered. Meyer<sup>58b</sup> has had a somewhat different experience with aminopterin. He reports that of 43 patients (adults and children) treated, 4 evidenced distinct clinical and hematologic improvement; 15 patients exhibited toxic effects requiring cessation of treatment; and 24 showed no change in their clinical course. Toxic effects noted by this observer include severe leukopenia, stomatitis, hypoplasia of the bone marrow, rectal bleeding, hematemesis, loss of hair, and hemorrhagic infiltration of the skin, in decreasing order of fre-

quency. He states that the beneficial and toxic effects could not be correlated with the dosage, nor with the simultaneous administration of liver extract or teropterin. Evidence that aminopterin is an extremely toxic agent is now increasing. The author knows of 2 adults who died after treatment; marked hypoplasia of the marrow was observed at autopsy.

Reinhard<sup>70a</sup> has treated 8 cases of acute leukemia with anti-folic acid derivatives—7 of these with aminopterin. No improvement was noted in 3 cases, but some symptomatic improvement occurred in 4. In none were the results impressive, although some reduction in the size of lymph nodes and spleen was occasionally observed. Toxic manifestations included stomatitis, but no evidence of aplasia of the marrow was seen.

*Myelokentric Acid*—Miller, Wearn, and Heinle<sup>61</sup> described myeloid and lymphoid metaplasia following injection of extracts of urine from leukemic patients. Much work has since been done on urine extracts, and Miller and Turner<sup>60</sup> have formulated an hypothesis of specific stimulators which act on the hematopoietic system. They term these substances myelokentric and lymphokentric acid. Miller *et al.*<sup>59</sup> have published data on the treatment of lymphoblastic leukemia with crude myelokentric acid. They treated 8 cases and report 13 partial remissions, but 7 of the 8 patients had died at the time of the report. Of interest, however, is the fact that autopsies on 5 of these patients supported the belief that the treatment had induced the remissions, for there was definite alteration in the histologic morphology as compared with the controls. This urine extract material is at present crude and relatively unobtainable, and the authors do not recommend this treatment, for no dosage schedule is established. This

work, however, is fundamental and a matter of great interest.

*Adrenocorticotrophic Hormone*—The influence of adrenal cortical secretion on the leukocytes<sup>10a</sup> and lymphoid tissue<sup>10b</sup> of normal mice has been studied by Dougherty and White. In man,<sup>10c</sup> they found less consistent results, but used a relatively small dose of cortical extract. Following injection of adrenotropic hormone in mice they found a decrease in total leukocytes, a decrease in the absolute number of lymphocytes, and an increase in the absolute number of polymorphonuclear leukocytes. A voluminous literature is now extant on this subject, which has been summarized by Valentine *et al.*<sup>51</sup> In 1943, Murphy and Sturm<sup>63a</sup> reported that adrenalectomy substantially increases the percentage of "takes" of a transmissible leukemia in rats. The following year these authors indicated that treatment with adrenal cortical extract increased the survival time when rats of a highly susceptible strain were inoculated with leukemic cells.<sup>63b</sup> Blood changes similar to those noted above for normal mice have been reported to occur in mice with spontaneous lymphogenous leukemia after injection of adrenal cortical extract.<sup>48</sup> Extensive degenerative changes of the immature lymphocytes in the thymus and lymph nodes were also evident. Levin, however, was unable to note any effect on a different strain of mouse lymphogenous leukemia when pituitary adrenocorticotrophic hormone was given.<sup>51</sup>

Nordenson<sup>66</sup> has reported an unsuccessful attempt to influence 2 cases of human chronic lymphogenous leukemia by injection of adrenal corticotrophic hormone, and Hills *et al.*<sup>55</sup> have published their observations on changes in the circulating leukocytes induced by pituitary adrenocorticotrophic hormone in man. It is improbable that these hormones will find any place in the therapy of human leukemia, but such stud-

ies are of importance in elucidating some of the factors concerned with hematopoiesis.

*Miscellaneous*—A variety of other drugs have been administered in leukemia, mostly to small series and with unimpressive results. Following a study of the effects of intravenous potassium antimonyl tartrate on the hemogram of rabbits,<sup>55</sup> Lucia reported that this drug caused the reduction of the white cell count of 6 out of 9 patients with leukocytosis of abnormal cells.<sup>54</sup> It is not useful in the therapy of leukemia.

Engelbreth-Holm and Stamer<sup>14</sup> have reported on their results with 9,10-dimethyl-1,2-benzanthracene in human leukemia. This is a highly toxic carcinogenic agent which had little or no effect in the myelogenous form of the disease. They state that at autopsy there was found remarkably little leukemic infiltration in 2 of their 4 acute leukemias so studied. Chronic lymphogenous leukemia responded "quite well" in 2 cases, aged 74 and 58.

Organo-metallic compounds of copper, nickel, and zinc have been reported to offer therapeutic possibilities in leukemia,<sup>26</sup> but the data are not impressive. One case of leukemia cutis has been published which authors feel may have been benefited by the administration of progynon B and diethylstilbestrol.<sup>73</sup> Tyrosinase has been said by Isaacs<sup>56</sup> to convert acute into chronic leukemia, but this is the single report of its usefulness. Colchicine<sup>46</sup> has been tried in acute myelogenous leukemia without very effective results, but it is probable that this agent deserves wider study because of its relation to purine metabolism. Davis<sup>52</sup> gave antireticular cytotoxic serum to 1 patient with chronic myelogenous leukemia, with repeated "responses" of the peripheral blood to each course of the serum. Contact with this patient has since been lost.<sup>57</sup> Avidin<sup>58</sup> and thiouracil<sup>52,53</sup> have

not been effective in the treatment of leukemia.

The effect of para-aminobenzoic acid in leukemia has recently been the subject of 2 reports. Zarafonitis *et al.*<sup>69</sup> found that sodium para-aminobenzoate, in doses of 2.0 to 4.0 gm. every 2 hours caused a striking lowering of the leukocyte counts in 5 patients with chronic myelogenous leukemia and 1 patient with the subacute form. They note that occasionally there was a decrease in spleen size but any objective improvement was slight and temporary. Two patients with chronic lymphogenous leukemia showed no essential decrease in leukocytes. Bichel,<sup>3</sup> on the contrary, found that para-aminobenzoic acid in doses of 2.0 gm. every 2 hours resulted in an abrupt rise in the leukocytes in 4 patients with chronic lymphogenous and in 2 patients with chronic myelogenous leukemia. The drug was stopped because of the complaints of soreness of the enlarged lymph nodes or spleen. Normal patients exhibited no significant variations in the leukocyte counts with this dosage.

Splenectomy has been abandoned as a useless form of treatment except in the unusual case complicated by the presence of an hemolytic anemia. In this event, Scott<sup>77</sup> advocates this operation as a worthy palliative procedure.

*Radiation Therapy.* That radiation therapy is useful in the treatment of chronic leukemia is an indisputable fact. Although the exact manner by which this effectiveness is accomplished is unproven, there is no doubt that radiation produces some clinical and hematologic improvement in the vast majority of patients with the chronic form of the disease. Just as certain, however, is the fact that eventually the disease becomes refractory after an unpredictable amount of radiation. It is primarily because of this development of radio-resistance that

search for chemotherapeutic agents is continued.

Under certain conditions it is probable that exposure to Roentgen rays can render man more susceptible to the development of leukemia. Data have been accumulated which show that the incidence of leukemia among radiologists is about 8 times that among other physicians.<sup>50</sup> More recent statistics supply additional evidence on this point.<sup>11</sup> Thus with radiation, as with many of the chemotherapeutic agents discussed above, we are using as treatment for leukemia an agent which can produce neoplasia.

There are several forms of radiation therapy now being used. Direct irradiation over the spleen, lymph nodes, or bones is the method most widely used. General body irradiation, or "spray" Roentgen-ray to the torso is not as widely available as the above because of certain physical factors required. Finally, irradiation through the use of radioactive elements is the least widely used because of the rigid requirements of measuring and handling which are necessary for their proper administration.

All who have had experience with the Roentgen treatment of leukemia recognize at least 3 cardinal principles. The first is that treatment must be individualized for each patient depending on the initial level of leukocytes and his response to therapy, without insistence upon a rigid, pre-arranged plan. Secondly, the patient should be given the least amount of irradiation that produces satisfactory results. Thirdly, the concept of "crossfire" should be utilized to minimize the skin exposure while giving therapeutic doses to the underlying tissue. It must be remembered that the effect of the Roentgen-ray treatment is not immediately apparent—there is a "lag" effect. For this reason lower dosage schedules are employed when the response of the pa-

tient is not known, when the level of leukocytes is not markedly elevated, and when there is evidence of a precipitous fall in the white count during treatment.

Forkner<sup>23</sup> has summarized the indications and contra-indications for Roentgen-ray therapy. Under no circumstances should the level of the leukocyte count alone be the factor which determines treatment. The indications are symptoms of anemia, hemorrhagic manifestations, evidence of a high basal metabolic rate, or pressure manifestations of an enlarged spleen or of enlarged lymph nodes.<sup>2</sup> The prime indication for the cessation of radiation therapy is a rapid fall in the white cell count or platelet count. In general, the development of a leukocyte count under 20,000 per mm.<sup>3</sup> or of a platelet count under 100,000 per mm.<sup>3</sup> is an absolute contra-indication to further therapy. Neither leukopenia nor thrombocytopenia are contra-indications to irradiation when they are not the result of former therapy. It is well recognized, however, that a patient with the "sub-leukemic" form of the disease has a relatively poor prognosis and is likely not to be benefited by treatment. If during the course of Roentgen therapy there occurs a marked anemia, rapid loss of weight, or a marked shift to the left with a great increase in the number of blast forms in the peripheral blood, treatment should be stopped.

**LOCAL IRRADIATION**—There are numerous treatment plans involving the use of direct or "spot" Roentgen-ray, but only a few will be mentioned. These concern the treatment of the chronic forms of the disease, for most reports in the literature indicate that Roentgen-rays are useless in acute leukemia. Lawrence,<sup>65</sup> however, is quoted as being in favor of radiation therapy in the acute form on the grounds that occasionally it does improve the condition. Hamann<sup>31</sup> feels that generally

it is ineffective in acute leukemia and should not be used except where some local distress is caused by lymphadenopathy or splenomegaly which may be relieved by treatment.

In chronic myelogenous leukemia Medinger and Craver<sup>57</sup> administer direct irradiation through 2 large portals over the spleen, 1 anteriorly and 1 posteriorly, in doses of 25r to 100r. These are repeated daily to a total dose of 200r to 300r to each of the portals. In the chronic lymphogenous disease their usual course consists of local therapy of 100r to 300r units to each area of external lymphadenopathy. The authors feel that survival is improved if this disease is first treated with local irradiation followed by total body therapy.

Popp and Watkins<sup>60</sup> suggest a larger number of portals be used in applying irradiation to the spleen. They outline 9 splenic portals, 4 anteriorly, 4 posteriorly, and 1 laterally and give daily doses to a total of 75 to 80r to each in subacute myelogenous leukemia. In the chronic form of this leukemia they suggest up to 225r be given to each portal, the dose to be determined by the response of the patient. If the patient manifests the sub-leukemic form, these authors suggest the cautious administration of up to 50 to 75r to each of the "small fields" mentioned above. In subacute lymphogenous leukemia they believe Roentgen therapy to be of doubtful value, but may give daily treatments of 75 to 100r to each field over areas of lymph node enlargement. Larger doses up to 225r per field per day are administered in chronic lymphogenous leukemia.

**TOTAL BODY OR WIDE-FIELD IRRADIATION.** This method of therapy is more recent in origin than the local method and is not available in many institutions because of the need of special facilities. It differs from the administration of local irradiation in that the

field covered is either the whole body or the torso, requiring a long target-skin distance. Medinger and Craver<sup>57</sup> have described the "Heublein" unit at the Memorial Hospital wherein a patient is exposed to continuous irradiation for a prolonged period. At the time of their report output of this unit was about 17r per day, with a target-skin distance of 3 meters. For the patient to receive 100r, an exposure of approximately 6 days was required. They felt that this method offered nothing over local irradiation in early chronic myelogenous leukemia, but that after the disease had become refractory to splenic irradiation this method occasionally brought about improvement. Craver<sup>61</sup> has recently concluded that the Heublein method of therapy seems to add to the survival period and to the periods of remission in chronic lymphogenous leukemia. Hamann<sup>31</sup> suggests the administration of a dose of 50r of "spray" irradiation in 5 fractions of 10r each. She concludes that when this type of therapy was administered to patients who had a decreased response to local irradiation, remissions were obtained, but no essential influence on the course of the disease was observed. When it was used initially, the effect shortly became less marked with subsequent use. The chronic lymphogenous leukemia patients responded to smaller doses of "spray" irradiation than did those with the chronic myelogenous form.

**RADIOACTIVE ISOTOPES — RADIOACTIVE PHOSPHORUS.** The use of P<sup>32</sup> in the treatment of leukemia was first detailed by Lawrence *et al.*<sup>59</sup> in 1939, and numerous reports on its usefulness have since been published. In 1946 Reinhard *et al.*<sup>71</sup> presented a critical summary of the literature, and analyzed their results in treating 155 patients with various blood dyscrasias. The interested reader is referred to this superb review. These authors discuss the ra-

tionale of the use of  $P^{32}$  in detail. Suffice it to say here that the tissues in which the greatest concentrations of radioactive phosphorus are deposited are those primarily involved in the leukemias and the lymph node diseases. Thus relatively high concentrations of radioactivity are obtained in the most advantageous sites, but, unfortunately, this differential distribution does not avoid damage to normal tissue. The beta rays emitted by  $P^{32}$  penetrate tissue to a depth of 0.7 cm. Of considerable advantage in the control of the radiation effects of this element is its half-life of 14.3 days.  $P^{32}$  may be given orally or intravenously. Studies on its absorption from the intestine indicate that it is safe to assume that about 75% of the oral dose is available to the body, but the intravenous route is the more widely used.

The dosage schedule must be varied to suit individual requirements, but the usual course recommended by Reinhard is as follows:

Day of Treatment	Dosage in Millicuries (I.V.)
1	1.0 — 2.0
3	0.5 — 1.0
6	0.5 — 1.0
10	0.5 — 1.0
14	0.5 — 1.0

The decision as to whether to use the smaller or the larger dose is based on the weight of the patient, the level of the white cell count, and the degree of hyperplasia of the bone marrow. If there is a very high leukocyte count, the above therapy is followed by 0.5 to 1.0 millicurie intravenously at weekly intervals until the level of approximately 30,000 cells per mm.<sup>3</sup> is reached. For lymphogenous leukemia those authors report that this same schedule is useful, but that usually administration must be discontinued sooner because of the more rapid fall in the leukocyte count. Sturgis<sup>19</sup> has outlined his treatment course using the oral route of ad-

ministration. He suggests 6 millicuries weekly until the white blood cell count falls to 40,000 per mm.<sup>3</sup> This is stated usually to require 2 to 4 treatments.

Several other schedules are in use in various clinics, but the above are cited as examples. In establishing a treatment course the availability of the  $P^{32}$  is an important factor, for larger doses may be given less frequently rather than smaller doses every few days as outlined above.

It is agreed that acute and subacute leukemias, including the monocytic variety, are not benefited by radioactive phosphorus.<sup>6c,20,71</sup> In chronic myelogenous leukemia, remissions from this form of therapy are as satisfactory as those following x-irradiation with the advantage of freedom from radiation sickness. Both Reinhard and Lawrence<sup>40</sup> feel that the length of life may be somewhat prolonged, but, if so, the increase is measured in terms of months. As mentioned earlier in this review, these data are difficult to evaluate with certainty. In general, the chronic lymphogenous variety of disease responds less well than the myelogenous form. Usually the reduction in the size of the lymph nodes is not as marked as that following Roentgen therapy, and there is no evidence that the patient's life span is increased. In both forms of chronic leukemia the evidence suggests that response to  $P^{32}$  is less favorable if x-irradiation had been given previously.<sup>16</sup>

As with other forms of radiation therapy administration of radio-phosphorus may be associated with leukopenia, thrombocytopenia, and anemia. A limiting factor which restricts its use to a considerable extent is the necessity for careful handling and rapidity of transport from the source to the patient.

**RADIOACTIVE SODIUM.** Evans<sup>17</sup> has reported on the use of radio-sodium in mice of the AK strain with various forms

of lymphadenopathy. Those animals with enlarged nodes and high leukocyte counts were found to be especially sensitive to the element, although there was no significant increase in the concentration of radio-sodium in the leukemic nodes over that in the blood. The author found it possible to reduce the white cell count without lowering the red cell count for longer periods by fractional rather than by single massive doses. Reinhard<sup>70</sup> has discussed the clinical aspect of the  $\text{Na}^{24}$  therapy. This isotope has a half-life of 14.8 hours, and emits both beta and gamma rays. It is distributed evenly in the body fluids, without selective uptake by bone or bone marrow. It is said to be easy to prepare and inexpensive. The author states that chronic leukemia responds as favorably to this isotope as to general body Roentgen radiation.

**RADIOACTIVE MANGANESE.** In 1946, Hahn and Sheppard<sup>30</sup> reported on the use of  $\text{Mn}^{52}$  in diseases of the lymphoid system. This isotope has a half-life of 6.5 days. It was given intravenously dispersed in a colloidal sol using gelatin as the supporting colloid. In a series of 24 administrations, fever and nausea had not been seen. The  $\text{Mn}^{52}$  selectively hits the lymphoid macrophage system, and the authors suggest its use in lymphogenous leukemia.

**RADIOACTIVE GOLD.** This element has been the subject of a brief report by Goodell *et al.*<sup>27</sup> who state that acute leukemias have responded poorly. In the chronic leukemias of adults, however, favorable results followed the intravenous administration of radio-gold.

**Symptomatic Therapy.** Although all of the effective agents discussed above truly should be included under this heading because of their relief of symptoms, certain forms of treatment are commonly useful which have no influence on the basic pathologic process. Of utmost importance for the comfort

of the patient who has acute leukemia is good mouth care. These patients often have moderate to severe infection of the pharynx and often have bleeding from the gums. Penicillin intramuscularly in the usual dosage is indicated when infection is present. For local care of the mouth astringent rinses are frequently of comfort by removing the taste of blood. Rinsing of the buccal cavity with a dilute solution of thromboplastin occasionally stops low grade bleeding from the gums. More active bleeding sometimes responds to the local application of gelfoam to the bleeding site. Allen *et al.*<sup>1</sup> suggest that toluidine blue, given intravenously in daily doses of 1.5 to 3.0 mg. per kg. body weight, may be useful in the control of the bleeding tendency when no ulcerations are present. The application of local x-irradiation to the hypertrophied gums of acute myelogenous or monocytic leukemias is usually considered inadvisable. The position occupied by transfusions in the treatment of the acute leukemias is a matter of very considerable difference of opinion. Some advocate multiple transfusions as supportive therapy, feeling that the life of the patient may be prolonged thereby. In the author's opinion it is difficult to establish this, but it is felt that if transfusions give the patient important symptomatic relief, their use should be considered. The patient's family should be advised, however, that such treatment is only palliative. Adequate sedation is of utmost importance, for commonly these patients are properly apprehensive.

In the chronic forms of the disease transfusions may be indicated as supportive treatment from the time that chemotherapeutic or irradiation therapy is begun until relief of symptoms occurs. Blood also should be readily available when any patient with the chronic form is to have any surgical procedure including dental extraction. During

periods of remission, these patients commonly are in need of no treatment whatsoever.

**Summary.** There is no evidence that any cures of leukemia have been effected. It is possible occasionally to induce temporary and partial remissions in the acute form of the disease by the use of aminopterin, nitrogen mustard, or crude myelokentric acid (in lymphoblastic leukemia). The chemotherapeutic agents of use in chronic myelogenous leukemia are Fowler's solution, urethane, and possibly benzol. Chronic lymphogenous leukemia responds seldom to Fowler's solution, and to urethane less well than the myelogenous form. Nitrogen mustard may be of value in the chronic leukemias, especially when they have become radio-resistant. The data indicate that

radiation therapy is still the most effective form of treatment, but that it is of little or no value in the acute form of the disease. Splenic irradiation in the chronic myelogenous form, and total body, "spray" to the torso, or direct Roentgen-rays to the enlarged lymph nodes in the chronic lymphogenous diseases are the techniques of choice for Roentgen therapy. Radio-phosphorus is apparently as good as Roentgen irradiation in chronic myelogenous leukemia, but is probably not quite as effective as the latter in chronic lymphogenous leukemia. Because of the frequency of spontaneous remissions and the wide variability in the natural course of both the acute and chronic forms of leukemia it is urged that the utmost caution be exercised in the interpretation of reports based on too few cases too briefly observed.

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# PHYSIOLOGY

## Proceedings

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

Session of October 19, 1948

**Studies on the Mechanism of Ammonium Lung Edema.** HAROLD KOENIG, M.D., M.S., Ph.D., and RUTH KOENIG, M.D. (Dept. of Anatomy, School of Medicine, Univ. of Penn). Toxic doses of ammonium chloride consistently produce acute pulmonary edema in rats, guinea pigs, less consistently in cats. (Koenig, H., and Koenig, R.: Anat. Rec., 100, 52, 1948). Changes in permeability of lung capillaries were studied by analyses for protein in the first edema fluid to appear in the trachea of 3 cats and 1 guinea pig. No protein was found in the edema fluid of 2 cats and the guinea pig, and only 0.7% in that of the 3rd cat. Thus, no gross increase in alveolar capillary permeability appeared during the early stages of this phenomenon in these animals. After anoxia set in, the alveolar capillaries began to leak abnormally, as evidenced by capillary hemorrhage and alveolar edema exudate which were always seen in the more advanced stages of this phenomenon.

The role of the nervous system in the genesis of this lung edema was investigated. Bilateral cervical vagotomy, atropinization and adrenalectomy did not block ammonium lung edema, but dibenamine, a sympatholytic drug, did. Decortication and anemic decerebration did not block lung edema, but spinal cord transection between C-6 and T-1 always prevented it. Mid-thoracic spinal cord section did not block

it in most animals, nor did severance of the cervical sympathetic chains. Therefore, the sympathetic nerve supply to thoracic viscera, activated at the brain stem level, appeared to be involved.

Systemic arterial hypertension occurred in ammonium intoxication. Its importance in this phenomenon was minimized, however, because: animals with spinal cord lesions which prevented edema still had hypertension; in one experiment, lung edema appeared without hypertension; and no evidence of left ventricular failure was ever seen at autopsy.

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**Cerebral Blood Flow and Metabolism in Normal and Toxemic Pregnancy.** MILTON L. MCCALL, M.D. (Depts. of Obstetrics and Gynecology, Jefferson Medical College and Hospital, and Philadelphia General Hospital). Using the quantitative nitrous oxide method of Kety and Schmidt, the cerebral blood flow and related metabolic functions of the brain were studied in normal pregnant women close to term as well as in patients with toxemia of pregnancy. In comparing mean values obtained from non-pregnant individuals with those from normal pregnant women, it was found that the latter had normal cerebral blood flow as well as comparable brain physiology as far as most of the other

cerebral functions studied were concerned. In pregnancy the volume percent of oxygen in the arterial blood was found to be definitely lower, however, while the oxygen utilized by the brain was the same as in normal non-pregnant persons.

Three types of toxemia were studied: toxemia superimposed upon essential hypertension, pre-eclampsia and eclampsia. In none of these was there evidence of significant deviation from normal in cerebral blood flow. In all, however, there was increased cerebral vascular resistance, the greatest degree being found in eclampsia. The oxygen utilization by the brain was normal in the nonconvulsive toxemias but in eclampsia this function was significantly decreased.

The older theories that there is a great reduction in the blood flow in the brain as well as deficient oxidation as the immediate causes of eclampsia are discussed in the light of the present study. Inasmuch as the cerebral blood flow and the oxygen brought to the brain are normal, these postulations are not substantiated. However, the brain itself was unable to utilize oxygen to a normal extent in convulsive eclampsia.

It has repeatedly been shown that there is capillary spasm in various portions of the body during this disease. The increased cerebral vascular resistance found in all toxemias adds another reason to believe that this is a generalized vaso-spasm.

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**Intra-articular Temperatures in Man.**  
STEVEN M. HORVATH, Ph.D., and J. L. HOLLANDER, M.D. (Dept. of Physical Medicine and Arthritis Section, Hospital of the Univ. of Penna.). A relatively simple method of obtaining intra-articular (knee, elbow and ankle) temperatures has been utilized to determine the degree of synovial hyperemia resulting from a disease process and to

evaluate the effect of various modalities of physical therapy on the joint tissues. Approximately 50 individuals, a few normals but mostly patients suffering from various arthritic diseases, have now been studied.

An excellent correlation has been observed between the joint temperature and the clinical state of patients with rheumatoid arthritis. Patients with degenerative joint disease were found to have higher intra-articular temperatures than would have been predicted from skin temperature over the joints and from their respective clinical states.

A number of procedures of physical therapy have been investigated. Passive movement of the affected joints resulted in a slight elevation of intra-articular temperature. Tentative classification of heating modalities is now possible and is apparently dependent on their ability to penetrate the tissues. Interesting reflex effects following application of hot or cold packs to a joint occurred. The application of hot packs results in a lowering of intra-articular temperature and, conversely, application of cold packs results in elevation of joint measure.

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**Non-Uniform Lung Ventilation.**  
WARD S. FOWLER, M.D. (Dept. of Physiology and Pharmacology, Graduate School of Medicine, Univ. of Penna.). Continuous analysis of  $N_2$  content (Lilly-Hervey nitrogen meter) and volume flow of alveolar gas expired after one inspiration of 99.6%  $O_2$  showed the  $N_2$  content to increase several percent as expiration continued. This indicates that (a) inspired gas is not evenly distributed throughout the functional residual air, and (b) with quiet breathing the poorly ventilated areas of the lung empty proportionately more later in expiration. In 38 of 40 healthy men, increasing  $N_2$  content was found in alveolar gas of a

quiet tidal expiration. The magnitude of the variation in alveolar  $N_2$  content, expressed as relative dilution of alveolar  $N_2$  by inspired  $O_2$ , decreased with larger inspired volume, smaller preinspiratory lung volume, inspiratory breathholding for 20 seconds, smaller expired volume, and rapid expiration. Less variation was found with hyperpnea (voluntary and post-exercise) than with quiet breathing. If a quiet expiration was immediately followed by a forced maximal expiration, a sudden increase in  $N_2$  content occurred coincident with the forced expiration, indicating a proportionately greater emptying of poorly ventilated areas by the forced expiration.

Unequal volume ventilation of the lungs has been thought to result from uneven lung expansion. However, if certain areas of the lung fill early in inspiration, they may receive more of the dead space gas than other areas which fill later. Alveolar composition differences may thus arise despite uniform volume ventilation. This possibility is supported by 2 findings. When inspiration began at the maximal expiratory position, (a) added inspiratory dead space increased the variation in alveolar  $N_2$  content, and (b) when a single inhalation consisted of  $O_2$  followed by air, the early expired alveolar gas had a higher  $N_2$  content than later expired gas.

### The Construction of Normal Standards for Cardiac Output in Man. J. M. TANNER, M.D.\* (Lab. of Therapeutic

Research, Univ. of Penna., and the Anthropological Lab., Dept. of Human Anatomy, Oxford University). The present per-weight and per-surface area standards for cardiac output, sharing a statistical fault common to all ration standards, give figures that are too high for large men and too low for small ones. New standards of the multiple regression type have therefore been developed, both for the ballistocardiographic and the catheterization methods. These methods can be shown to agree excellently when the statistical relations between them are examined in the light of the coefficients of reliability of each. The ballistocardiograph standards are based on data upon 50 students obtained by the author when working in Dr. Starr's laboratory, and previously communicated to this Society (1); and on the large series of Starr and Schroeder<sup>2,3</sup> covering 174 persons of wide age range. To bring the ballistocardiograph figures into line with the Cournand<sup>4</sup> catheterization values when Starr's recommendation<sup>5</sup> to omit the aortic cross-section is followed, the constant 33 in the ballistocardiograph formula has been replaced by the approximate value 100, making the formula

$$SV \text{ (ml.)} = 1002 \frac{\text{area I} + \text{area J}}{c}$$

when the areas are measured in millimeter-seconds.

A biometric examination of all published series of cardiac output values has led to the following new standards:

#### For the Starr ballistocardiograph

- Estimate Stroke Volume (ml.) = .53 Surface Area (sq. in.) - .85 Heart Rate (per min.) - .85 Age (years) + 75 for Men.  
 = .21 Surface Area (sq. in.) - .40 Heart Rate (per min.) - .45 Age (years) + 80 for Women.  
 Estimate Cardiac Output (1/min.) = 2.6 S.A. - .055 Age + 3.0 for Men.  
 = 2.1 S.A. - .045 Age + 3.1 for Women.

#### For catheter standards, means at the level of Cournand's series<sup>4</sup> have been assumed giving:

- Estimate Stroke Volume (ml.) = .53 S.A. - .85 H.R. - .65 Age + 71 for Men.  
 = .53 S.A. - .75 H.R. - .65 Age + 64 for Women.  
 Estimate Cardiac Output (1/min.) = 2.6 S.A. - .042 Age + 2.5 for Men.  
 = 2.6 S.A. - .042 Age + 2.8 for Women.

\* Present address, Sherrington School of Physiology, St. Thomas Hospital, London SE1.

These equations should be regarded as major terms in longer, more accurate expressions, and are subject to revision as new data accumulates; they apply only between the ages of 20 and 70. The standard error of estimate of stroke volume is about 11 ml. and for cardiac output about 0.8/1 min. A value differing from the standard by twice this amount should be regarded as probably abnormal.

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# BOOK REVIEWS AND NOTICES

**THE DIABETIC'S HANDBOOK.** By ANTHONY M. SINDONI, JR., M.D., Chief, Department of Metabolism, Phila. General Hospital. With 6 contributing authors. Pp. 194; 7 ills. New York: Ronald Press, 1948. Price, \$3.00.

THIS handbook opens with a section listing the common questions asked by diabetic individuals. To these, didactic answers are given. The next sections deal with symptoms, complications, insulins, foods, laboratory tests, specific care, and general hygiene. The book contains much necessary information but much that is superfluous, thus interfering with proper emphasis of the more important aspects.

Certain errors detract from the value of the book. Thus on page 42 it is stated "mg. (milligram)—one tenth of a gram, or approximately 2 grains"; and on page 53 in the table, one finds that insulin shock "Follows within a few minutes after insulin injection." (The facts are correctly set forth in the discussion.) Furthermore, on page 6 and elsewhere the impression is given that only "25 to 30 percent of the cases are due to heredity." Such phrases as "cheating on their diet" and "The trouble with many persons is they do not drink sufficient water" are frequent. Despite such deficiencies, the book can serve as a reference textbook for the patient and as a useful adjunct to the physician's guidance.

F. D.

**SUCCESSFUL MARRIAGE.** Edited by MORRIS FISHBEIN, M.D., and ERNEST W. BURGESS, Ph.D. Pp. 547; 13 figs. New York: Doubleday, 1947. Price, \$6.00.

ALTHOUGH the number of marriage-counseling books being published is rapidly increasing, the merits of this volume make it very welcome. The efforts of 38 well-qualified authors are grouped in the following: 1. preparation for marriage; 2. the marriage; 3. conception, pregnancy and childbirth; 4. the child in the family; 5. social problems of sex and marriage, with each section subdivided into 6 or more parts. The editors are to be commended for their choice of contributors and for fine editing. The authors, themselves, have covered their respective problems with noteworthy clarity and a directness and simplicity of language which is laudatory.

Every phase of the marriage problem is mentioned and discussed, although some articles are necessarily brief. The text, which is

(600)

refreshingly readable, seems to be pitched at a collegiate level. Each chapter contains a list of references, and a well-organized index is included. The volume can be recommended to the practitioner, to young people contemplating marriage, and for use in the classroom.

G. R.

**GIVE THEM A CHANCE TO TALK: Handbook of Speech Correction for Cerebral Palsy.** By BERNEICE R. RUTHERFORD. Foreword by JOHN F. POHL, M.D. Pp. 116; 9 ills. Minneapolis: Burgess Publishing Co., 1948. Price, \$2.75.

FOLLOWING brain injury, defective muscle movements and speech defects may be observed, which in the group of cerebral palsied children, have been all but incurable. In such disorders Mrs. Rutherford's pioneer work affords techniques whereby remarkable improvement may be obtained. For the spastic, athetoid, or ataxic, defective movements the methods include proper manipulation of the speech musculature; visual stimulation through watching one's movements in a mirror; critical listening to one's speech; strengthening and controlling the tongue muscles; strengthening the neck muscles and gaining control of the muscles of breathing; learning to synchronize breathing; correction of unnecessary and undesirable habit patterns.

N. Y.

**PRACTICAL THERAPEUTICS.** Edited by MARTIN EMIL REHFUSS, M.D., F.A.C.P., F. KENNETH ALBRECHT, M.D., and ALISON HOWE PRICE, A.B., M.D., with 13 Contributors. Pp. 824; 70 ills. Balt.: Williams & Wilkins, 1948. Price, \$15.00.

THIS is a book which the general practitioner will find invaluable. It tells what to do and how to do it, and gives thousands of useful prescriptions. There is a section devoted to symptomatic therapy, but most of the book is devoted to the treatment of specific disorders. Inevitably, there is a certain amount of repetition, but this is not necessarily a disadvantage; one does not have to search through the book to find the desired information. The layout is well planned; the type is large and easily read. Unfortunately there are numerous typographical errors and misplaced decimal points which might prove embarrassing or worse to the physician who is not conversant with both the apothecaries and the metric system of drug dosage.

H. H.

**HANDBOOK OF PRACTICAL BACTERIOLOGY.**

By T. J. MACKIE, M.D., Prof. of Bacteriology, Univ. of Edinburgh, and J. E. McCARTNEY, M.D., Fellow Rockefeller Inst., New York. 8th ed. Pp. 624. Balt.: Williams & Wilkins, 1948. Price, \$7.00.

OF THE volume's 3 parts: An introduction, including discussions of the general biology of micro-organisms and immunity in relation to practical bacteriology. A second part on bacteriological technique, is followed by a description of micro-organisms (including filtrable viruses) and their bacteriological diagnosis. There are numerous diagrammatic illustrations and tables but no photographs. As a practical manual, the text contains many items of useful information not found in other books of this nature. The chapters on viruses and pathogenic fungi, although brief, are also helpful. The descriptions of the diseases caused by pathogenic micro-organisms should be particularly useful for non-medical laboratory personnel. However, the advisability of including such subjects as discussion of the serologic tests for syphilis and a few protozoan parasites, which are better described in works of different nature, is open to question.

R. N.

**HEMOSTATIC AGENTS, WITH PARTICULAR REFERENCE TO THROMBIN, FIBRINOGEN AND ABSORBABLE CELLULOSE.**

By WALTER H. SEEGER, M. S. Ph.D., Prof. of Physiology, Wayne Univ. Coll. of Med., and ELWOOD A. SHARP, M.D., ScD., Director, Department of Clinical Investigation, Parke, Davis and Company. Pp. 131; 27 ills. Springfield, Ill.: Charles C Thomas, 1948. Price, \$4.50.

THIS monograph fills a definite need for surgeons, dentists and others, who wish to take advantage of recent developments in the field of hemostasis. It condenses in a short space and in very readable form the practical and much of the theoretical background for the use of thrombin, fibrinogen, oxidized cellulose, fibrin foam, and gelatine sponge. The section on blood clotting largely avoids controversial matters and so might seem incomplete to some readers. However, it does set forth clearly those points which the authors regard as established. The chapters on thrombin, fibrinogen, and oxidized cellulose are especially good.

J. R.

**HEMOLYSIS AND RELATED PHENOMENA.**

By ERIC PONDER, M.D., D.Sc., The Nassau Hospital, Mineola. Pp. 398; 69 ills. New York: Grune & Stratton, 1948. Price, \$10.00.

THIS volume is the third of a similar nature published during a period of 25 years by a

very active worker and a recognized authority in the field of hemolysis and the general properties of the red cell. Like its predecessors, it brings together in one place the results of the author's own extensive and important researches up to the date of publication, and would be of value for this reason alone. But in addition it provides a stimulating discussion of the more important work of others in the same general field, its references to the literature including more than 600 titles. Though dealing primarily with the subject of hemolysis, it very properly devotes about half of its pages to a description of the general properties of the cell which is hemolyzed. Readers other than specialists will doubtless find this portion of the book of greatest interest; but no serious student of the erythrocyte can afford to be unacquainted with its entire contents.

M. J.

**VENOUS THROMBOSIS AND PULMONARY EMBOLISM.**

By HAROLD NEUHOF, M.D., Clinical Prof. of Surgery, Columbia Univ. Pp. 159. New York: Grune & Stratton, 1948. Price, \$4.50.

THIS monograph on the related subjects of acute venous thrombosis and pulmonary embolism is based chiefly on the author's experience on a board designed to study the rôle of pulmonary embolism in hospital deaths. It draws heavily on the extensive literature of the subject, but maintains its own opinions capably. Conclusions are based on a wide knowledge of the problems in surgery, gynecology, and medicine, and are illustrated by numerous case histories. It is refreshing to see the author treat cases individually, rather than by general rule. He gives, for instance, his reasons for or against anticoagulant therapy, or venous ligation, in any one case. No physician or surgeon can read this monograph without gaining a respect for the danger of venous thrombosis in both surgery and medicine, nor will he avoid using prophylactic measures to help prevent venous thrombosis. Nor will he any longer "treat" this dangerous disease by the old-fashioned rest and elevation, alone.

H. M.

**THE SKULL, SINUSES, AND MASTOIDS. A HANDBOOK OF ROENTGEN DIAGNOSIS.**

By BARTON R. YOUNG, M.D., Prof. of Radiology, Temple Univ. Medical School. Pp. 328; 141 ills. Chicago: Year Book Publishers, 1948. Price, \$6.50.

THIS most recent and final volume in the series is an excellent contribution to the small group of books which lend themselves to easy reference by the active practitioner. The many



illustrations are of superior quality and relate to the text on the facing page, an arrangement which has the fault of requiring reading of an entire page for clarification at times, yet allows an unusual volume of material to be covered in a manner which may still be read in continuity. The written presentation is clear, related to clinical rather than didactic use, and the completeness should be quite adequate for general practitioners and most specialists. The conciseness of explanation makes it also of value to the radiologist and neurosurgeon. The elaborations of pneumographic, angiographic and special apparatus techniques, such as body section roentgenography, may well be obtained from other sources by the specialists primarily concerned.

R. C.

AN INTEGRATED PRACTICE OF MEDICINE. A Complete General Practice of Medicine from Differential Diagnosis by Presenting Symptoms to Specific Management of the Patient. By HAROLD THOMAS HYMAN, M.D. Four volumes and Index. Pp. 4336; 1184 ills.; 305 in color. Phila.: W. B. Saunders, 1947. Price, \$50.00.

This is not merely a new work, but a new kind of work. It attempts: (a) to put into one publication all that a practitioner needs to know about the various ramifications of specialized as well as general medical practice and about the underlying facts from the basic sciences; and (b) to arrange, collate and integrate that material so that it be easily available when presenting symptoms furnish a key. The emphasis lies in the arrangement and cross-references that make the 25 sections of the book parts of a unified whole rather than isolated texts in a special medical field. The concept is brilliant and constitutes a major advance in medical writing.

The execution of the idea, however, is not yet all that it should or can be. In arriving at this conclusion, the Reviewer has done three things: systematically read through most of the work; used it daily for a year in the teaching as well as the practice of internal medicine; consulted with a number of general practitioners who have used it in their practice.

The usual criticism by the general practitioners was that the information was inadequate and that recourse to other texts was frequently necessary. This would seem remediable only by making the work larger, and some thought that should be done. It could be done, but there remains the need to draw a line somewhere between a "working" text and a reference or encyclopedic text.

The Reviewer himself found the work a most useful one. While the Author had primarily the general practitioner in mind, it would seem that the work in its present form is even more useful to the specialist, almost regardless of his field of interest. This is true because the publication offers concise up-to-date information on fields about which the specialist has not thought or read for a long time, and on whose book-shelves the most recent information is in the textbooks which he acquired as a medical student. Let it be remembered that in addition to internal medicine the work covers psychiatry, ophthalmology, otology, rhinolaryngology, urology, gynecology, obstetrics, pediatrics, orthopedics, dermatology, minor surgery, anesthesiology, major surgery, convalescence and rehabilitation, basic science review, physical diagnosis, dietetics, radiology, pharmacology, therapeutics, and dentistry!

Good points include the many and excellent differential diagnostic tables and the numerous illustrations. Some of the color pictures are too "colored" (e.g., the rose spots of typhoid fever). The index is well prepared and there are many timely cross-references.

At times one gets the impression that topics have been covered by the "scissors and paste" route, rather than on the basis of first-hand knowledge. Filariasis is not transmitted by mites, is not diagnosed by dark-field examination, nor with any reliability by skin tests, nor is it attended by generalized edema as stated in the text. No one familiar with the disease would have made these statements. Other comparable instances could be cited. The illustrations have also been gathered from many sources, a commendable practice under the circumstances. Future editions and a greater number of skilled collaborators should rectify such minor short-comings.

The Author is to be congratulated on the monumental work which he has conceived and produced.

R. K.

## NEW BOOKS

*British Encyclopedia of Medical Practice.* Editor-in-chief, Rt. Hon. LORD HORDER, G.C.V.O., M.D. Pp. 539. With *Cumulative Supplement*. Pp. 377. London: Butterworth, Ltd., 1948. Price .....

CRITICAL surveys of 14 branches of the physicians' work are presented, together with a section on Recent Developments in Pharmacology and Therapeutics. More than half the space is occupied by a few hundred abstracts.

*Advances in Carbohydrate Chemistry.* Vol. 3. Edited by W. W. PIGMAN, PH.D., M. L.

WOLFROM, PH.D., and (for the British Isles) STANLEY PEAT. Pp. 424. New York: Academic Press, 1948. Price, \$8.50.

THIS volume continues the record of the previous volumes in presenting authoritative articles upon a variety of special topics. There are presented 11 reviews dealing with stereochemistry, biochemistry and organic chemistry of carbohydrates (including cellulose) written by qualified investigators from Great Britain, Germany, Sweden and the United States. Of particular interest are the chapters on (1) The Molecular Constitution of Cellulose (J. Compton); (2) Isotopic Tracers in the Study of Carbohydrate Metabolism (S. Gurin); (3) Products of the Enzymic Degradation of Starch and Glycogen (K. Myrback); (4) The Polysaccharides of Mycobacterium Tuberculosis (M. Stacey and P. W. Kent), and (5) The Chemistry of Streptomycin, (R. U. Lemieux and M. L. Wolfrom).

H. V.

*Principles Governing Eye Operating Room Procedures.* By EMMA I. CLEVENGER, R.N., Supervisor Eye Operating Room, New York Eye and Ear Infirmary. Pp. 215. Illustrated. St. Louis: C. V. Mosby, 1948. Price, \$5.50.

THIS is a valuable book to have in all eye services in the hospital. It is a reference book and is well indexed. Whenever a nurse, or for that matter a surgeon, wishes to find the technical details of instruments or other equipment connected with an eye operating room, an excellent exposition can be found in this book. This is very time-saving, for such details are not easily to be obtained in any library and can be found only by consulting instrument makers' catalogues, which is cumbersome. The book naturally leans toward the operating techniques used in the New York Eye and Ear Infirmary, but this is by no means a disadvantage. The book should be in the possession of every eye operating room nurse.

F. A.

*The Medical Clinics of North America.* Mayo Clinic Number. Pp. 303; 49 ills. Phila.: W. B. Saunders, 1948. Price, \$15.00 a year.

FOLLOWING 5 papers on the clinical features and treatment of the types of congenital heart disease that are particularly amenable to surgical treatment, a variety of subjects are reviewed: diseases of the thyroid, ulcerative colitis, megacolon, peritoneal lavage, the treatment of infectious diseases, pernicious anemia.

W. J.

*Modern Trends in Diagnostic Radiology.* Edited by J. W. McLAREN, M.A., M.R.C.S., St. Thomas's Hospital. London. Pp. 464;

381 ills. New York: Paul B. Hoeber, 1948. Price, \$12.00.

THIS is a collection of scientific papers by 32 authors most of whom are British. A wide variety of subjects is included, ranging from such fundamentals as "The Meaning of Speed and Contrast in X-ray Materials" and "Safety in the Radiodiagnostic Department" to "Pulmonary Hemosiderosis", "Foetal Abnormalities", "Aspects of Hydatid Disease" and "The Law Relating to the Practice of Radiology". The articles in general are well written. Other informative contributions not previously mentioned are "Radiographic Diagnosis of Tumors of the Pharynx and Larynx" (F. Baclesse), "Radiology of the Heart" (P. Wood), "Some Aspects of Ventriculography and Encephalography" (Erik Lysholm) and "Cerebral Angiography" (Arne Engset and Kristian Kristiansen). Certain portions are disappointing but the book in general is a worthwhile contribution and should be of interest to radiologists and radiology students.

C. P.

*The 1947 Year Book of Pediatrics.* Edited by ISAAC A. ABT, D.Sc., M.D., Emeritus Prof. of Pediatrics, Northwestern Univ. Medical School, with ARTHUR F. ABT, M.D., Associate Prof. of Pediatrics. Pp. 454; 91 ills. Chicago: Yearbook Publishers, 1948. Price, \$3.75.

LIKE all its predecessors, this issue of the Year Book of Pediatrics consists of a useful digest of current articles of pediatric interest gathered from many sources, arranged and classified so as to be conveniently accessible for reference. The volume is dedicated to Dr. Isaac Arthur Abt, noted teacher and author and editor of the Year Book of Pediatrics since its origin 46 years ago, who celebrated his 80th birthday in full vigor on December 18, 1947.

I. W.

#### NEW EDITIONS

*A Manual of Practical Obstetrics.* By O'DONEL BROWNE, M.B., M.A.O., Rotunda Hospital. Dublin. 2d ed. Pp. 267; 218 figs.; 8 plates. Balt.: Williams & Wilkins, 1948. Price, \$9.00.

*Gray's Anatomy of the Human Body.* Revised and edited by CHARLES MAYO GOSS, M.D., Prof. of Anatomy, Louisiana State Univ. 25th ed. Pp. 1478; 1263 ills., mostly in color. Phila.: Lea & Febiger, 1948. Price, \$14.00.

*The Hair and Scalp: A Clinical Study.* By AGNES SAVILL, M.A. 3d ed. Pp. 304; 54 ills. Balt.: Williams & Wilkins, 1944. Price, \$4.75.

THE contents of this small, attractive volume are as satisfactory as its external appearance. It includes both a scientific background of the subject of hair, especially as far as its physiology and chemistry are concerned, and also presents detailed directions for the care of normal hair and scalp and a discussion of their disorders. This practical, carefully prepared and well illustrated book deserves continued and unqualified recommendation. H. B.

*Neuroanatomy.* By FRED A. METTLER, M.D., Ph.D., Assoc. Prof. of Anatomy, College of Physicians and Surgeons, Columbia Univ. 2d ed. Pp. 536; 357 ills., 33 in color. St. Louis: C. V. Mosby, 1948. Price, \$10.00.

IN THIS edition important additions and changes have been made, while the general plan remains the same. New material has been added on the arterial supply and venous drainage of the different parts of the brain and spinal cord. The description of the thalamic subdivisions has been made more understandable by a series of diagrams in which many of the subdivisions of the thalamus have been correlated with specific areas of the cerebral cortex. The results of the most recent research have been utilized in this presentation of the thalamus and will be novel to most students. Other interesting topics are the innervation of the meninges, the spinal mechanism of micturition and the connections of the basal ganglia. There are 47 pages of bibliography but little reference is made to these in the text. This book gives one of the most comprehensive and detailed accounts of the minute structure of the central nervous system that is available for students and others interested in the subject.

W. A.

*Diseases Affecting the Vulva.* By ELIZABETH HUNT, M.D., Hon. Consulting Dermatologist, South London Hospital for Women. 3d ed. Pp. 211; 36 ills., 19 color plates. St. Louis: C. V. Mosby, 1948. Price, \$7.50.

THIS edition contains considerable additions, especially to the sections on treatment. These are detailed in the preface. Although the Reviewer regards this as a useful volume, there are a number of concepts which are open to question. For example, syphilis "is considered to be an allergic condition resulting from inoculation with *spirochaeta pallidum*". In a book appealing to general practitioners, bicarbonate-glycerine treatment (p. 121) for rodent ulcer might better be omitted. Aside from such minor points, this is a worthy successor to the previous editions. H. B.

*Conference on Metabolic Aspects of Convalescence.* 15th Meeting. Edited by EDWARD C. REIFENSTEIN, JR., M.D., Sloan-Kettering Institute, New York. Pp. 163; 35 ills. New York: Josiah Macy, Jr., Foundation, 1948. Price, \$2.25.

THE first part of this publication is devoted to a symposium on the physics, chemistry, and clinical application of isotopes in medicine. Many fundamental facts are given which are of utmost importance to research workers in this field. The second part on the endocrinological control of metabolism includes articles on steroid affects on bone metabolism; adrenocorticotrophic hormone therapy in panhypopituitarism; intestinal excretion during intravenous alimentation, and corticoid excretion in Cushing's syndrome. In all, 24 papers are presented.

G. R.

*An Introduction to Dermatology.* By G. H. PERCIVAL, M. D., Grant Professor of Dermatology, Univ. of Edinburgh. 11th ed. Pp. 349; 233 ills. Balt.: Williams & Wilkins, 1947. Price, \$9.00.

TO THOSE of us brought up on earlier less dressed-up editions of the late Sir Norman Walter's *Introduction*, Percival's product evokes mixed feelings. This edition is entirely rewritten but retains the original intent to present a useful, if not complete, system. Rarities are not stressed and Walker's histopathologic sketches have been replaced by colored photomicrographs, mostly in low-power magnification. There are few typographical errors. This edition continues to provide the practitioner and student with a pleasant introduction to a difficult branch of medicine.

H. B.

*Gardiner's Handbook of Skin Diseases.* Revised by JOHN KINNEAR, O.B.E., T.D., M.D., M.R.C.P. (Ed.), D.L. Lecturer in Diseases of the Skin, St. Andrew's Univ. 5th ed. Pp. 250; 80 ills., 20 color plates. Balt.: Williams & Wilkins, 1948. Price, \$4.50.

IN THIS edition of a previously well-received book, the author has placed much in little space. He attempts to classify cutaneous diseases on an etiological basis and uses a diagrammatic method for representing the histopathology of many of the processes described. The text is well written, the illustrations are clear and the volume contains but few statements not in keeping with current practice. Although the now deprecated local use of penicillin is espoused, the author wisely decries the employment of sulfonamides topically.

H. B.

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## ORIGINAL ARTICLES

### THE MILLIKAN OXIMETER IN THE RECOGNITION AND TREATMENT OF ANOXEMIA IN CLINICAL MEDICINE

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THE accurate methods available for determining a given patient's need for oxygen therapy, and for assessing the results of oxygen administration, have been too cumbersome for general use at the bedside. The attending physician has been forced to use one or more of the following rather crude indications: (a) The presence of a disease which may produce anoxemia, (b) The presence of dyspnea, (c) The presence of visible cyanosis (sometimes difficult to assess accurately),<sup>3</sup> and (d) The apparent clinical response to a trial of oxygen therapy.

The Millikan Oximeter<sup>9</sup> affords a simple and accurate means for determining the changes in arterial oxygen saturation, at the bedside, without the discomfort of arterial puncture, or the difficulties of conventional gas analysis. We have used it on the medical wards of the Hospital of the University of Pennsylvania to assess the need for

oxygen therapy in the individual patient, and to determine the method of oxygen administration best suited to his needs.

**Methods.** 1. *The Oximeter:* The oximeter consists essentially of a small "ear unit" and a galvanometer. The ear piece contains an electric bulb, light filters, and a photo-electric cell. It fits over the pinna of the ear with the bulb in front, the filters and cell behind. The heat generated by the bulb dilates the arterioles of the ear and increases the blood flow sufficiently to make the ear blood equal, in oxygen content, to arterial blood. The light generated by the bulb penetrates the ear and strikes the photo-electric cell. The filters and cell have such characteristics that variations in the amount of oxyhemoglobin within the blood vessels of the ear are recorded continuously on the galvanometer. Present models of the instrument cover only half the potential range of saturation; hence the galvanometer is graduated from 50 to 100%. There is a time lag of 5 seconds in the

galvanometer. With these limitations, Millikan has shown by comparison with hundreds of simultaneous arterial punctures, that the instrument is accurate within 3 to 7%.<sup>9</sup>

Although percentage changes in oxygenation can be read directly from the instrument, absolute values can only be obtained by one of two procedures: (a) while a normal subject is breathing 100% oxygen, the galvanometer is adjusted to a reading of 100%; subsequent changes in the same subject during the same experiment will be shown in absolute figures; (b) with an abnormal subject whose capacity to oxygenate his blood completely in an atmosphere of pure oxygen is questionable, one must set the galvanometer at some arbitrary figure and take one simultaneous arterial blood sample for gas analysis; the mathematical difference between the arbitrary setting and the actual saturation at that moment can then be used as a constant factor for correcting subsequent readings during the same run.<sup>10</sup>

In the following experiments, method (a) was used in all normal subjects. In some abnormal subjects (Cases 26 and 36, and in a patient with the Tetralogy of Fallot, not included in the Tables) method (b) was used. In the remainder, the oximeter readings were recorded without a simultaneous determination of arterial oxygen saturation. This limited our ability to assess the original degree of anoxemia in these subjects. However, as will be indicated below, the percentage rise in the oximeter reading following oxygen therapy, in addition to affording an accurate method of assessing the effects of oxygen administration, permits certain deductions concerning the presence of anoxemia.

**2. Subjects:** A total of 46 individuals was studied. Ten of these were hospital employees or patients who showed no clinical evidence of anoxemia or of any disease which might interfere with the oxygenation of the blood. The remaining 36 were considered to be potentially or actually anoxicemic as a result of diseases of the heart, lungs, or both. These subjects were classified accordingly as: I. "nor-

mal"; II. cardiac disease; III. pulmonary disease; and IV. mixed. This classification was made on the basis of the clinical findings, supported, in a few instances, by information obtained at necropsy. Obviously there is considerable overlapping in the last 3 groups; since there is usually some pulmonary involvement in advanced cardiac disease and vice versa. In each instance the assignment to a group depended on our estimate as to which factor was the predominant cause of the anoxemia.

**3. Procedure:** With the patient at rest in bed or in a wheel chair and breathing room air, the oximeter was attached to the ear. After the bulb was lit, 15 minutes were allowed to elapse to permit "warming up" of the instrument and full dilation of the ear vessels. Pulse rates and respiratory rates, blood pressure readings, and circulation times\* (Decholin arm-tongue) were determined during this basal period. At the end of the 15 minutes, the galvanometer was adjusted to the clinically estimated arterial saturation (from 96% in the normal group down to 60% in very cyanotic individuals). Oxygen was then administered and the galvanometer readings recorded every 15 seconds until there was no further change. The maximum rise was reached within 5 minutes in all but a very few instances, and could be maintained indefinitely. After continuing oxygen administration from 5 to 60 minutes, it was discontinued abruptly and the rate and degree of fall in the oximeter reading was recorded. Pulse, respiration, and blood pressure were checked repeatedly throughout the test.

Since our main purpose was to compare the maximal rise in arterial oxygen in different individuals, it was necessary to administer to all a uniform and high concentration of oxygen. The B. L. B. (Boothby, Lovelace, Bulbulian,<sup>2</sup>) mask proved an acceptable method for doing this. Direct measurements of samples withdrawn from the mask showed an oxygen concentration of 90 to 97%. All of the graphs and most of the data reported here are based on the rise in oximeter reading observed when the pa-

\* In 18 of the 36 abnormal patients.

tient suddenly changed from breathing room air to breathing oxygen through a B. L. B. mask.

In most subjects the test described above was repeated several times on the day of the first experiment. In many, it was repeated on several occasions subsequently, in order to correlate changes in the oximeter response with changes in the patient's condition.

In certain instances in addition to the routine test with the B. L. B. mask, oxygen was administered in lower concentrations, and the oximeter response was compared to that of the routine test. The Lambertson-Godfrey hood<sup>8</sup> was used

(3) An "increased oximeter response" is a rise of more than 5%. This we take as an indication of anoxemia, i.e., that the arterial oxygen must have been below 95% while the subject was breathing room air.

**Results.** 1. *Normals* (10 subjects). The patients in this group ranged in age from 16 to 71 years, four having been 50 or over. Two of the older patients had peripheral vascular disease, and another was moderately hypertensive. None had symptoms nor showed any signs of cardiac failure or pulmonary disease. On breathing 90 to 97% oxygen from the B. L. B. mask, the maximal increase in arterial

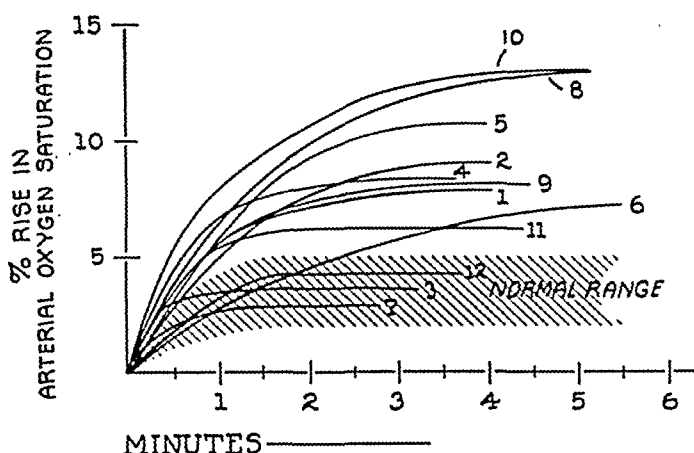


FIG. 1.—Acute Cardiac Infarction. The numbers at the ends of the curves refer to the cases of this sub-group.

in a number of such experiments and proved capable of delivering controlled concentrations ranging from 30 to 85% by direct measurement. Oxygen was administered by nasal catheter in a number of other instances. We assumed that an oxygen inflow of 7 liters per minute by nasal catheter properly placed in the oropharynx gave an inspired oxygen concentration of from 40 to 50%.<sup>1a</sup>

4. *Terminology:* In the rest of this paper we will use the following terminology. (1) A subject's "oximeter response" signifies the rise in the galvanometer reading when he changes from breathing room air to breathing 90 to 97% oxygen in a B. L. B. mask.

(2) A "normal oximeter response" is a rise of 5% or less. A normal oximeter response does not rule out anoxemia (see discussion).

saturation (oximeter response) ranged from 2 to 5%.<sup>†</sup> This "normal" range is blocked out in all of the following figures as a standard of comparison.

2. *Cardiac Disease* (22 patients). This group is subdivided into (a) Acute Cardiac Infarction and (b) Congestive Heart Failure.

(a) *Acute Cardiac Infarction* (Figure 1) (12 patients; Cases 1 to 12). The patients in this group had typical histories and characteristic clinical and electrocardiographic findings of acute myocardial infarction. In 3, the diagnosis was confirmed at necropsy. These 12 patients were selected solely on the basis of their diagnosis, not because they had clinical evidence of anoxemia. As shown in Figure 1, their oximeter responses varied from 3 to 13%. Nine, or 75%, showed an increased oximeter response. Pulmo-

<sup>†</sup>Comroe and others<sup>1a,6</sup> have done a similar test on a larger series of normals and have demonstrated a slightly greater range (2 to 6%).

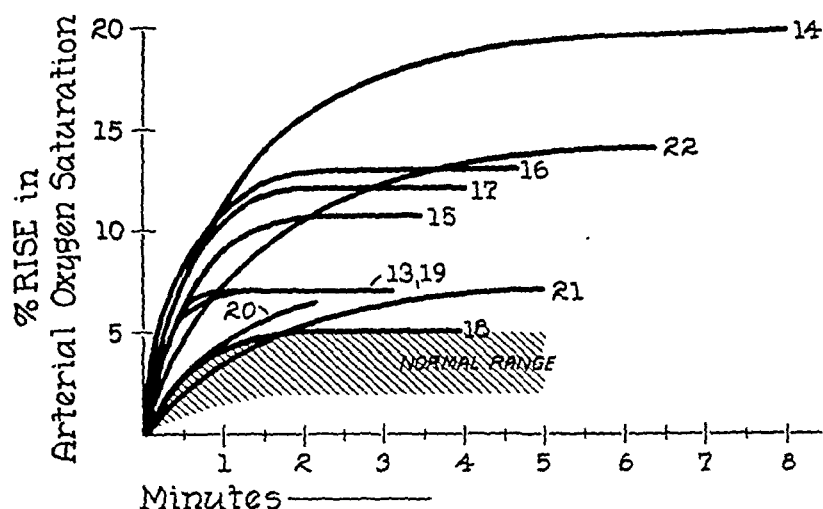


FIG. 2.—Congestive Heart Failure

nary congestion (6 cases) and, or, shock (3 cases) were the 2 most obvious factors which were present and possibly responsible for the anoxemia in these subjects. Of the 3 patients having responses of 10% or more, Case 5 was in shock with marked pulmonary edema, Case 8 was in shock, his lungs were clear to physical examination, Case 10 was in moderately severe congestive heart failure with pulmonary congestion. However, 4 patients (Cases 1, 6, 9, 11) showed an increased oximeter

response (*i. e.* anoxemia) without demonstrable signs of shock or more than a few râles at the lung bases. We were unable to find any means of predicting the oximeter response in these patients. Moreover, there was no constant correlation between the oximeter response and cyanosis, pulse rate, respiratory rate, or precordial pain.

(b) *Congestive Failure* (Figure 2)(10 patients; Cases 13 to 22). Valvular disease, old myocardial infarction, and

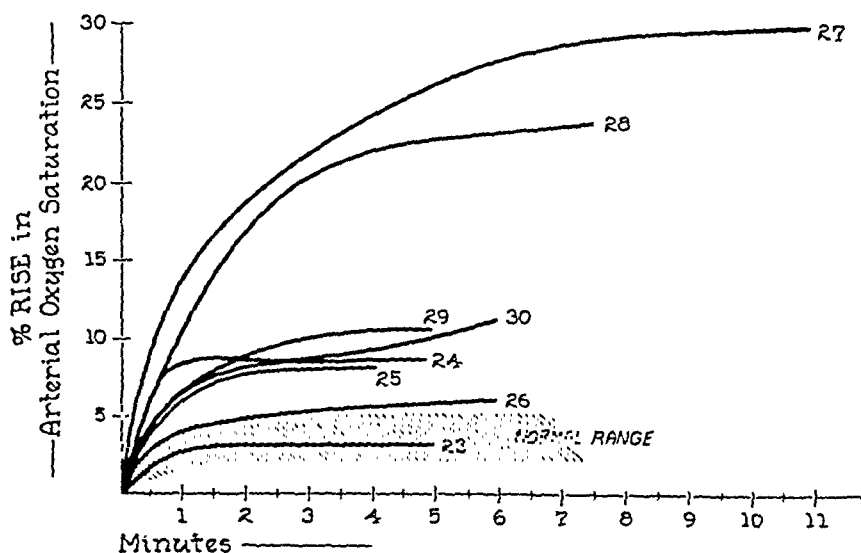


FIG. 3.—Pulmonary Disease

hypertension were the underlying causes of congestive failure in these patients. Five of them showed an oximeter response of from 10 to 20%; four rose from 6 to 10%; only one had a response within the normal range (5%). All those individuals whose response was greater than 10% were moderately to markedly cyanotic before being given oxygen. However, others who appeared to be equally cyanotic did not respond in this manner.

We were unable to find any criterion, such as cyanosis, pulmonary congestion, dyspnea, or orthopnea, which would enable us to predict reliably the degree of response. For instance, Patients 13 and 14 were quite similar in their clinical manifestations. Patient 13 was a man of 56 years with hypertension and pulmonary edema; Patient 14 was 65 years of age with degenerative heart disease and pulmonary congestion. Both were cyanotic and orthopneic. Patient 14 showed a

20% response. Patient 13 gave a 7% response.

Three patients, whose responses exceeded 10%, died, while only one, whose rise was under 10%, succumbed.

3. *Pulmonary Disease* (Figure 3) (8 patients; Cases 23 to 30). All these patients showed clinical and X-ray evidence of disease of the lungs. On the basis of their oximeter response, they may be divided into 2 groups: (a) four whose response was less than 10%, and (b) four whose response was greater than 10%. The 4 with less than 10% response all had chronic pulmonary disease. All complained of a marked limitation of their exercise tolerance, but none had dyspnea or cyanosis at rest. Three of these (Patients 24, 25, 26) had emphysema. The fourth (Patient 23) had extensive bilateral silicosis.

All of the patients who showed responses of 10% or more had cyanosis,

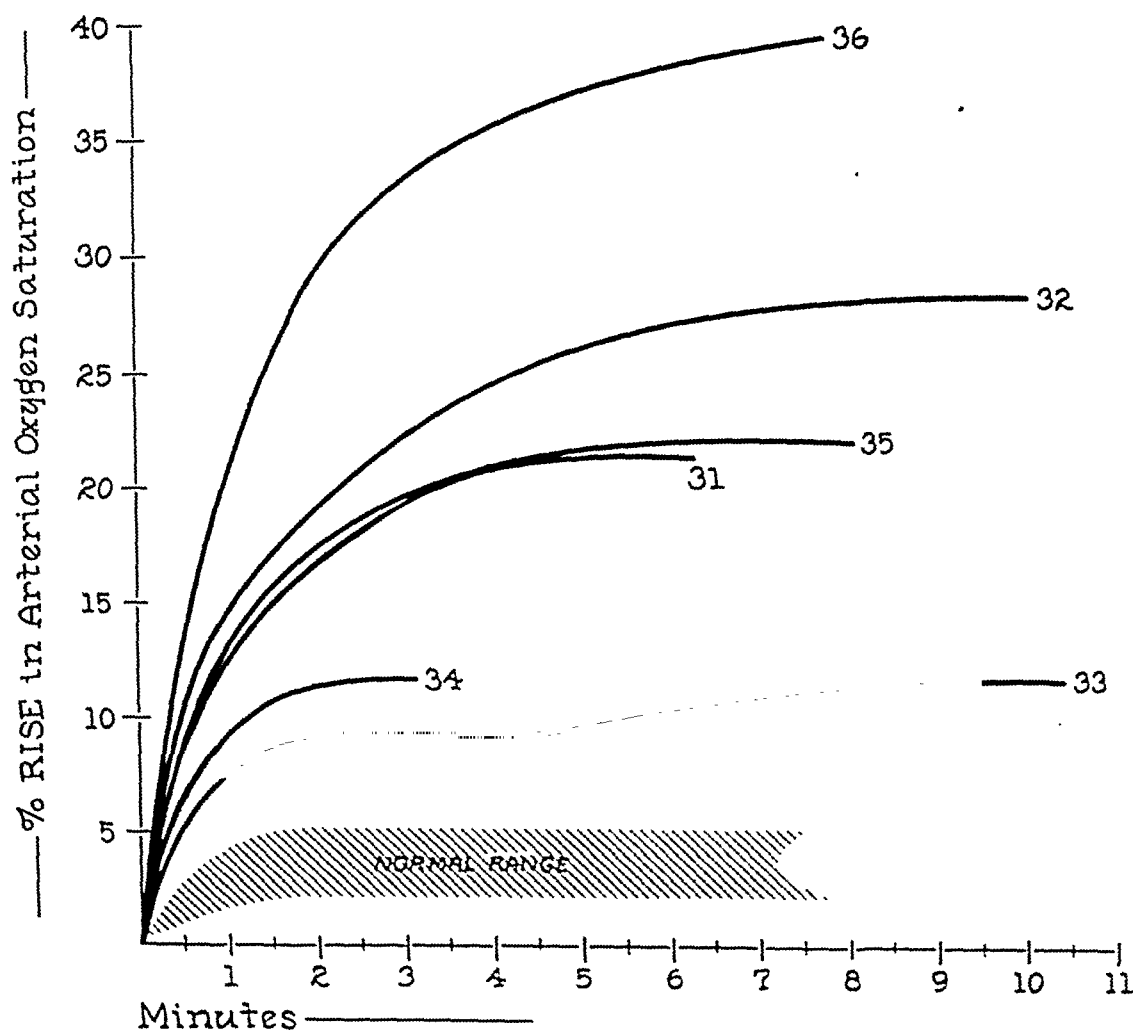


FIG. 4.—Mixed Group



orthopnea, and tachypnea. Subject 27 had severe emphysema and bilateral bronchopneumonia. Patient 28 had a spontaneous pneumothorax with 30% collapse of the right lung complicating a chronic lesion at the right base which was thought to be due to either congenital cystic disease or bronchiectasis. Patient 29 had a lobar pneumonia involving the right middle and lower lobes with secondary atelectasis and pleural effusion. The fourth patient (No. 30) had an extensive bronchogenic carcinoma invading the right middle and lower lobes, confirmed at necropsy. The first 3 patients in this subgroup improved clinically with appropriate therapy and their oximeter re-

sponses, some of them to a very striking degree. This was not unexpected in view of the fact that all were cyanotic. Being a very heterogeneous assortment with only their anoxemia in common, no generalizations can be made regarding prognosis or treatment except for their need of oxygen. Actually the 2 with the smallest oximeter responses are the only ones who have died.

**Discussion.** During the war, the Millikan oximeter was used mainly in the study of normals. It has also been used in studying special types of cardio-respiratory problems.<sup>7,11</sup> The experiments reported in this paper demon-

TABLE 1. OXIMETER RESPONSES WITH VARYING INSPIRED OXYGEN CONCENTRATIONS.

	<i>B.L.B. Mask</i> 90-97% oxygen		<i>Nasal Catheter</i> 7 liters/ min. 40-50% oxygen		<i>L-G Hood</i> O <sub>2</sub> concentration insp. air	
	<i>Case</i>	<i>% response</i>	<i>% response</i>		<i>% response</i>	
Myocardial Infarction	2	9.	6			
	4	9.5	5			
	5	10.	—	80% oxygen conc.	10	
	6	7	4			
	8	13.	—	80% oxygen conc.	10	
	10	12.	7			
	12	4	3.5			
Congestive Failure	17	14	8			
	19	7	—	80% oxygen conc.	6	
	20	7	6			
Pulmonary Disease	27	30	20			
	28	20	—	60% oxygen conc.	20	
				40% oxygen conc.	15	
Mixed Group	31	20	10			
	33	12	8			
	34	11.5	5.5			
	36	46	—	30-33% oxygen conc.	35	

sponses diminished as they improved, while the last showed an increase in his oximeter response on a second test a few days before death.

4. *Mixed Group* (Figure 4) (6 patients; Cases 31 to 36). This group consists of patients with a combination of pulmonary and cardiac disease. Two subjects (Nos. 35, 36) had chronic disease of both systems, the other four were patients with chronic heart disease and acute pulmonary complications. As shown in Figure 4, all members of this group showed definitely increased oximeter re-

sponses, some of them to a very striking degree. This was not unexpected in view of the fact that all were cyanotic. Being a very heterogeneous assortment with only their anoxemia in common, no generalizations can be made regarding prognosis or treatment except for their need of oxygen. Actually the 2 with the smallest oximeter responses are the only ones who have died.

strate that the instrument is useful in management of patients, since it affords a simple, convenient and rapid method for assessing the results of oxygen therapy at the bedside. Direct measurements of arterial oxygen are helpful in experimenting with this instrument, and the oximeter does not entirely replace such measurements. However, when arterial puncture and gas analysis are contra-indicated or unavailable, the oximeter response in a given patient is an indicator of the

degree of benefit to be expected from oxygen administration, and may be used to determine the concentration of oxygen best suited to the individual case.

The following table shows the oximeter responses obtained with varying inspired oxygen concentrations.

These figures show that, whereas in general the largest oximeter responses were obtained with the highest concentrations of inspired oxygen, certain patients (Nos. 27, 28 and 36) showed very striking responses to lower concentrations.

Thus in selected cases, the relatively low inspired oxygen concentrations such as are obtainable in an oxygen tent or by nasal catheter, appear to be therapeutically effective. However, the selection of such cases on clinical grounds alone does not seem possible.

If it had not been for the oximeter, the patient described in case report 36 might not be alive today. This 44 year old man with advanced pulmonary fibrosis had been admitted to the medical wards 4 times between March 1946 and January 1947 for congestive heart failure. In February, 1947 he was readmitted very ill with anasarca, orthopnea and cyanosis. He was tested with the oximeter and a remarkable response (45%) was obtained with 90-97% oxygen administered by B. L. B. mask. This was checked by means of chemical determinations of arterial oxygen saturation, and found to be accurate. Then by means of the oximeter it was determined that as little as 33% oxygen in the inspired air would maintain a 30% to 35% rise in the oximeter reading. Consequently, he was placed on continuous oxygen by nasal catheter at 6 liters per minute, digitalization was maintained, diuretics discontinued, and his fluid intake was not restricted. A marked clinical improvement occurred. At the end of 3 weeks he was dis-

charged, free of edema, and with no dyspnea while walking slowly. During the eleven months since then, he has led a quiet ambulatory life at home, remaining free of congestive heart failure by using nasal oxygen throughout the night, and stopping it during the day. Digitalis has been continued. Thus the oximeter led to the discovery that a marked rise of arterial oxygen saturation could be obtained in this patient by the relatively low inspired oxygen concentrations obtained by nasal catheter; this resulted in the institution of a practical and effective method of treatment.

One rather unusual reaction to oxygen therapy was encountered which we believe is worth while reporting. Case 27, a 58 year old male with emphysema and chronic bronchitis, was admitted to the hospital acutely ill, with extreme cyanosis; temperature 100.2°, dyspnea and orthopnea. X-ray of his chest revealed an extensive bilateral bronchopneumonia in addition to the pre-existing pulmonary disease. He was conscious, but slightly disoriented on admission. Oxygen therapy was started coincident with the oximeter run. After 5 minutes of breathing 90 to 97% oxygen, the patient became deeply comatose. His blood pressure rose to 180/100 from a preoxygen level of 130/70. He showed a 30% oximeter rise. When oxygen was stopped, he regained consciousness and his blood pressure fell to its admission level. This series of events could be repeated at will. With nasal oxygen at 7 liters a minute, his oxygen saturation rose approximately 20% and he did not become comatose. Consequently, it was decided to use nasal oxygen for treatment instead of a B. L. B. mask. With massive antibiotic therapy and nasal oxygen, he made a rapid recovery. After resolution of his bronchopneumonia, as judged by both X-ray and

TABLE 2. ACUTE CARDIAC INFARCTION

	Diagnosis	Electrocardiogram	Temperature	Pulse	Respirations	Blood Pressure	Pulmonary Congestion	Cyanosis	Oximeter response to inhalation O <sub>2</sub> 90-97%	Result
1) J. Lev, white male, 70 yrs.	Ac. card. infarct.	Ac. post. lat. infarct.	99.2	90	20	134/76	+	+	7½%	Discharged impr.
2) S. Ang, white male, 57 yrs.	Ac. card. infarct.	Ac. post. lat. infarct.	97	60	16	90/60	0	+	40-50% 9%	Discharged impr.
3) L. Str, white male, 70 yrs.	Ac. card. infarct.	Rec. post. infarct.	120	Chyenne Stokes	90/70	+	+	0	3½%	Died. Recent and old myoc. infarct.
4) O. Fuh, white male,	Ac. card. infarct.	Ac. ant. infarct.	134	24	147/84	+	+	+	40-50% 5%	Died. Necropsy refused.
5) J. Fink, white male, 70 yrs.	Ac. card. infarct.	No evidence recent damage	135	26	80/70	+	+	+	80% O <sub>2</sub> 10%	Died. Recent big myoc. infarct.
6) M. Mer, white female, 64 yrs.	Ac. card. infarct.	Suggestive but not diagnostic ac. infarct.	98.6	66	20	155/90	+	0	7%	Discharged. Further symptoms and E.C.G. changes.
7) B. Bus, white male, 57 yrs.	Ac. card. infarct.	Ac. ant. infarct.	120	18 fibrillating	118/70	+	+	?	2½%	Discharged impr.
8) J. Fini, white male, 58 yrs.	Ac. card. infarct.	Ext. ant. infarct.	116	24	90/80	0	+	+	80% O <sub>2</sub> 10%	Died. Massive card. infarct.
9) H. Kam, white male, 50 yrs.	Ac. card. infarct.	Ac. ant. infarct.	100	104	20	120/70	+	+	8%	Discharged impr.
10) M. Lia, white male, 62 yrs.	Ac. card. infarct.	Ac. ant. myoc. infarct.	99	100	40	110/80	+	+	10-50% 7%	Died. Necropsy refused
11) B. Sue, white male, 58 yrs.	Ac. card. infarct.	Ac. ant. lat. myoc. infarct.	98.6	56	16	136/80	0	+	6½%	Discharged impr.
12) J. Gol, white male, 68 yrs.	Ac. card. infarct.	Ac. myoc. infarct.	86	26	160/80	0	0	0	4%	Discharged impr.

\* Pulmonary Congestion  
 + = few basal râles.  
 ++ = moist basal râles  
 +++ = râles over lower ½ lung fields  
 ++++ = râles over entire lung fields  
 + Cyanosis graded + to ++++ on basis of inspection only.

clinical signs, a final oximeter run revealed a response of 12½%. He was still slightly cyanotic as he had been on examination one year previously. Such unusual reactions to oxygen therapy have been described in individuals with chronic anoxemia. These patients are thought to develop a tolerance to oxygen lack by means of changes in the cellular metabolism of their cerebral tissues. Thereafter a sudden increase in arterial oxygen tension may give rise to such symptoms of central nervous system disturbance as somnolence, semi-coma or coma which may last for several days.<sup>1b</sup>

An oximeter response which is significantly greater than the normal may be accepted as evidence that anoxemia is present. However, the converse is not true—a normal oximeter response does not rule out the presence of anoxemia. For instance, a lesion, in which blood enters the left side of the heart without first coming into contact with aerated lung, will produce anoxemia, which will not show a striking response to the inhalation of oxygen. We have observed this failure to respond in a very cyanotic child with the Tetralogy of Fallot. Arterial puncture revealed an arterial oxygen saturation of 53% while breathing room air. Oxygen inhalation of 5 minutes' duration gave a rise of only 5% in the oximeter reading. Another subject with an undiagnosed type of cyanotic congenital heart disease showed only a 6% response to oxygen therapy despite deep cyanosis.

Stagnant anoxemia due to slow circulation, in which blood leaves the heart with a normal oxygen saturation, but passes slowly through the capillary bed and returns to the heart with a very low saturation, theoretically would not show a marked response to oxygen inhalation. This might explain why the responses seen in acute cardiac infarction were relatively small.

We do not believe that a small or "normal" oximeter response necessarily signifies that oxygen therapy is useless if other indications for it exist. In such critical situations as severe myocardial infarction, even a slight increase in the oxygen available to the damaged tissues may be beneficial. When such a patient is given a high concentration of oxygen to breathe, a certain quantity of oxygen is dissolved physically in the plasma in addition to the measurable increase in oxyhemoglobin. The sum represents a substantial increase in the oxygen available for utilization.<sup>2</sup> However, a patient with a small oximeter response is probably less likely to derive benefit from oxygen therapy than a patient with a great response.

The studies reported in this paper indicate that many patients with disease of the heart, lungs, or both, show an abnormally high oximeter response. In general, those with cardiac infarction showed the smallest oximeter response; the patients with congestive failure, small to moderate response; those with pulmonary disease varying response. The most striking results were seen in patients with a combination of pulmonary and cardiac disease. Thus the diagnosis of the pathological process underlying the anoxemic state may give some hint as to the probable response to oxygen. However, there are many individual variations.

In an attempt to improve our ability to predict the response in any given individual we have tried to correlate various clinical signs with the observed response in these patients:

(a) *Cyanosis*: In the groups with pulmonary edema, extensive primary pulmonary disease, and in the mixed group, there was a fairly good correlation between the degree of cyanosis and degree of response. However, cyanosis, except in marked degree, is difficult to evaluate.<sup>3</sup> Patient 26 was thought to be definitely cyanotic by



two of the authors. Yet he showed only a 6% response to 97% oxygen and his arterial oxygen saturation while breathing room air was found to be 94.3% by direct measurement. Conversely Patient 35, in whom cyanosis was regarded as mild, showed a very marked response (22%).

(b) *Pulmonary congestion:* There was no correlation between the oximeter response and the presence of a few pulmonary râles, but frank pulmonary edema was always associated with an increased response, though in some cases the increased response was minimal (Cases 13, 20 and 21).

(c) There was no correlation between blood pressure and the oximeter response except in a few patients with myocardial infarction and in Case 27 (see above).

(d) The Decholin arm-tongue circulation time was determined in a total of 18 patients. It was found to be prolonged in 7 cardiac patients, normal in 7 out of 8 pulmonary patients, and prolonged in 3 of the mixed group. It was of no obvious value in predicting the oximeter response.

(e) Pulse rate was markedly lowered in only 6 patients during the test (Nos. 9, 10, 31, 32, 33, 35). Respiration was significantly lowered in two (Nos. 16, 30). Therefore, these two signs were not frequently enough altered to be reliable indicators. However, it must be emphasized that the period covered by each test was brief and more significant alteration, especially in pulse rate, might have been noted had the test period been longer.

Thus cyanosis and pulmonary edema when present were usually associated with a significant increase in oximeter response. In their absence, no other signs proved reliable for purposes of prediction.

The value of oxygen therapy to prevent anoxemia in anaesthesia, post-

operatively and in elderly individuals with pulmonary disease, is well established. In such cases the oximeter may be of value in detecting small degrees of anoxemia, although ideally oxygen therapy should be instituted prior to the development of anoxemia.

The oximeter may be used in negroes, but preliminary tests suggest that the magnitude of the change in the oximeter reading is less than the actual change in arterial saturation.

**Summary.** (1) Changes in arterial oxygen saturation were measured by means of the Millikan Oximeter in 10 "normal" subjects and 36 patients with cardiac and, or, pulmonary disease (a) breathing room air and (b) breathing 90 to 97% oxygen.

(2) The normal "oximeter response" which we observed as a result of the subject changing from room air to 90 to 97% oxygen was 5% or less.

(3) Patients suffering with a combination of both pulmonary and cardiac disease showed the most marked oximeter response to oxygen therapy. Those with extensive pulmonary disease, or pulmonary edema secondary to cardiac failure, showed moderate response. Patients with acute cardiac infarction showed relatively small responses, although the majority (75%) were above the normal range.

(4) Some patients show remarkable oximeter responses to relatively low inspired oxygen concentrations.

(5) There are certain clinical factors (type of disease, presence of pulmonary congestion, cyanosis) which are of some help in predicting and in evaluating the results of oxygen therapy. However, in many instances the results of oxygen inhalation cannot be predicted, nor can they, as a rule, be accurately evaluated by ordinary clinical methods. The oximeter permits the evaluation of results; it has not helped much in teaching us to predict the results.

TABLE 4. PULMONARY DISEASE

	Diagnosis	Temperature	Pulse	Respirations	Blood pressure	Cyanosis†	Oximeter response to inhalation O <sub>2</sub> 90-97% varying %	Result
23) H. Krc, white male, 62 yrs.	Silicosis upper 2/3 both lung fields. Emphysema bases, Morning sputum. No other symps.	98°	70	20	113/78	0	3%	Discharged. Cond. unchanged
24) J. Hax, white male, 37 yrs.	Emphysema, chronic tracheobronchitis. Dyspnea on exertion.	98°	60	28	120/75	0	8½%	Discharged. Cond. unchanged
25) P. Con, white male, 59 yrs.	Emphysema, severe. Dyspnea on exertion	98°	86	26	104/68	+	8%	Discharged. Unimpr.
26) D. Man, white male, 71 yrs.	Emphysema, chr. bronchitis. Dyspnea on exertion.	98	80	22	150/85	Considered definitely cyano.	6% Vanslyke art. oxy gen. sat. 94.5%	Discharged. Unchanged
27) J. Fir, white male, 38 yrs.	Emphysema, severe, chr. bronchitis. Diffuse blact. br. pn., cond. critical.	100°	103	38	133/70	+++	30% Deep coma on 40-50% 20% 90-97% oxygen	Discharged improved. Oximeter response 12½% on discharge.
28) J. Sig, white male 60 yrs.	Spontan. pneumothorax 30% collapse rt. lung. Emphysema, cystic dis., of lt. base. Cond. critical	98	62	24	133/80	+++	20% 20% with 60% oxygen 15% with 10% oxygen	Discharged, impr. On 3 subsequent admissions during next 12 mon., progressively severe dyspnea on exertion, marked cyanosis, congest. ht. failure (cor. pulmonale).
29) W. Ste, white	Lobar pneumonia, rt. lower lobe.	First day 104.2 10th day 98.6 13th day 98.6	100 90 80	28 20 20	108/60 150/80 150/80	++ + 0	11% 9% 5%	Discharged. Cured.
30) J. Sch, white male, 69 yrs.	Bronchogenic ca. involving rt. lower lobe.	Day of admission 98.6 21 days after admission 110.	96 44	20 44	120/70	+	10%	Died. Necropsy. Bronchogenic ca. rt. lower lobe, br. pn., abscesses.

\* Pulmonary Congestion

+ = few basal riles,  
 ++ = moist basal riles,  
 +++ = riles over lower ½ lung fields  
 ++++ = riles over entire lung fields  
 † Cyanosis graded + to ++++ on basis of inspection only.





(6) An oximeter response greater than normal indicates the presence of anoxemia, and signifies that therapeutic benefit may be expected from oxygen therapy, roughly commensurate with the degree of the response. A normal oximeter response does not rule out anoxemia. It suggests that oxygen therapy will probably be less strikingly beneficial. However, a normal oximeter response does not neces-

sarily indicate that no benefit will be obtained from oxygen inhalation.

(7) Thus the oximeter enables the physician at the bedside to determine the effectiveness of oxygen therapy more accurately than by clinical evaluation, and in certain instances permits him to recognize the presence of anoxemia which might otherwise have been overlooked.

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# STUDIES ON BLOOD HISTAMINE

## PARTITION OF BLOOD HISTAMINE BEFORE AND AFTER CLOTTING IN HEALTH AND DISEASE STATES\*

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THE presence in the peripheral blood of a substance having pharmacologic and toxicologic properties indistinguishable from histamine is a matter of considerable interest. That such an H-substance does exist in measurable quantity has been repeatedly demonstrated and Code and Ing<sup>5</sup> have isolated from whole blood what is apparently the crystalline dipicrate salt of histamine itself. The term "blood histamine" will be used throughout this report to denote the active substance responsible for contracting guinea pig ileum when blood has been extracted according to Code's<sup>8</sup> method for determining blood histamine.

Under ordinary circumstances the blood histamine resides in the cellular component of blood, where it exists in bound form and is pharmacologically inactive. The erythrocytes have been demonstrated to have a relative poverty of histamine activity as have by inference the blood lymphocytes, since normal or low values have been found in lymphatic leukemia.<sup>20</sup> The blood platelets in most species studied are also poor in histamine activity but in the rabbit it is possible these elements may contain considerable quantities of histamine.<sup>12,16,31</sup> The myeloid leukocyte, however, contains the majority

of the blood histamine in most animals and in man<sup>4,5,6,7,24</sup> and the blood of human patients with myeloid leukemia may possess histamine activity a hundredfold or more greater than that of blood of normal subjects.<sup>6,28</sup>

Under special circumstances, the blood histamine may be liberated from its inactive form in the cells to a free state in the plasma or serum where it is pharmacologically active. Appreciable amounts of free histamine are found in blood plasma after anaphylactic shock in certain species,<sup>9</sup> and trypsin injected intravenously is capable of liberating histamine from blood cells<sup>3</sup> as well as from other tissues.<sup>20</sup> Histamine may pass from cells to plasma in vitro when peptone<sup>30,13</sup> or proteolytic enzymes such as trypsin<sup>10,27,19,3</sup> or papain<sup>21</sup> are added to blood, or when specific antigen is incubated for a short period with sensitized blood.<sup>14,15</sup> Plasma histamine also increases during reactive hyperemia and muscle contraction in man.<sup>2</sup>

It has also been repeatedly stated that histamine release from cells to serum occurs when blood coagulates. Many investigators have noted pharmacologic activity in serum which was not present in plasma. It is not suitable to review here the literature relative to such differences between serum and

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plasma in view of the numerous discussions already available. Suffice it to say that while part of the activity present in serum has been clearly shown to be due to substances other than histamine,<sup>18,32</sup> the latter has none the less been suspected of being partially responsible for the pharmacologic properties observed. Code<sup>4,5</sup> in 1937 found that 69 to 90% of the total blood histamine in rabbits passed from cells to serum when blood was allowed to clot and in a single experiment demonstrated histamine in human serum. The results in rabbits are of course somewhat clouded by the possibility that the platelets of this species may contain appreciable amounts of histamine. Grana and Rocha e Silva<sup>12</sup> have reported confirmation of Code's observations and Selle<sup>25</sup> in an extensive review has stated that histamine liberation from cells is associated with coagulation of blood. Anrep and co-workers<sup>1</sup> could not find histamine in human serum and Reid<sup>18</sup> has recently concluded that in the serum of man (and in certain animal species) the main substance stimulating guinea pig jejunum is not histamine.

It was the purpose of this investigation on human subjects (1) to determine the effect of coagulation on the partition of histamine between cells and serum, and (2) to investigate the blood histamine levels in certain disease states and if possible to correlate the differential leukocyte picture with the level of blood histamine. In connection with the primary objective it was felt that reports of histamine liberation as a phenomenon associated with the coagulation of blood were of considerable interest and worthy of further investigation. There was no obvious explanation as to why the entrapment of leukocytes within a fibrin mesh should result in loss of their histamine unless some biochemical process incident to blood clotting was responsible. The

fact that proteolytic, trypsin-type enzymes have been suspected by some<sup>11,26</sup> to play an important rôle in the coagulation of blood and that similar enzymes have been demonstrated as capable of releasing histamine from blood cells to plasma fostered the hope that studies on the partition of histamine after coagulation might give some clue as to the presence or absence of such enzyme activity during clotting.

**Methods.** In the partition studies, blood was withdrawn without stasis into a clean dry syringe from the antecubital veins of 4 normal adults, one patient with leukocytosis and bladder malignancy, and 2 adults with chronic myelogenous leukemia. In one of the patients with chronic myelogenous leukemia 2 separate determinations were made—one shortly before and one shortly after a course of radiation. Blood was always carefully handled to avoid trauma in so far as possible. Suitable samples of whole blood (never less than 10 cc. in the case of normal individuals) were placed directly and without anticoagulants into trichloroacetic acid. In each instance the remainder of the blood obtained was placed in a clean glass flask containing glass beads and defibrinated by gentle rotation of the flask. The clotted defibrinated blood was then transferred, beads, fibrin and all, to a clean tube and centrifuged at 2500 to 3000 r.p.m. for 8 to 10 minutes. Suitable serum samples were obtained by pipetting off the serum down to 1-2 cc. above the cell-serum interphase. These serum samples were likewise placed in trichloroacetic acid and treated in a manner identical to that employed with whole blood. The amount of serum available for extraction was never less than 7 cc. in the case of normal individuals, was 3.5 and 7.5 cc. respectively in the 3 determinations made on the leukemic blood and 5 cc. in the determination made on the patient with bladder malignancy and leukocytosis. In the leukemic patients, a well defined white cell layer separating erythrocytes from serum was readily apparent when the clotted defibrinated blood was centrifuged. In all determinations made on these patients additional samples were taken from this leukocyte rich layer after defibrination and centrifuging. It was possible to determine in this way if the leukocytes still retained their histamine after clotting. In all instances the cells, serum and clot were allowed to remain in contact approximately 25 to 30 minutes from the time clotting began.

In every experiment except one, total and differential leukocyte counts were made on each whole blood specimen assayed. Total leukocyte counts were made on each serum sample with one exception, and on the leukocyte rich samples obtained from leukemic blood after defibrination.

In an associated group of studies, whole blood histamine values were obtained from subjects with a wide variety of disease states. In such studies 5 to 10 cc. of whole blood were placed directly in trichloroacetic acid without the addition of anticoagulants. All specimens in each experiment were extracted by Code's modification<sup>8</sup> of the method of Barsoum and Gaddum and assayed on atropinized terminal guinea pig ileum suspended in 2½ to 3 cc. of Tyrode's solution. Serum samples were extracted in the same manner as whole blood in order to be certain as nearly as possible that the activity assayed was due entirely to histamine.

it is realized that if histamine were liberated nearly quantitatively from cells to serum, each cc. of serum from the normal individuals should contain the amount of histamine originally present in slightly less than 2 cc. of whole blood. While the results are sufficiently definite in normal subjects, the determinations are given added significance by the enormous differences in serum and whole blood histamine observed in individuals with myelogenous leukemia. In the latter cases, it was also possible to demonstrate that the myeloid leukocytes still contained large amounts of histamine *after* defibrination. It appears reasonable to state that in man there is little or no libera-

TABLE 1 — HISTAMINE DETERMINATION IN HUMAN SUBJECTS ON WHOLE BLOOD BEFORE CLOTTING AND ON SERUM AFTER CLOTTING AND DEFIBRINATION

Patient	Age	Diagnosis	Sample	Leukocyte counts per cu. mm.	Histamine in gamma per cc.
W.N.V.	29	Normal	Whole Blood		0.079
			Serum		0.015
R.P.	32	Normal	Whole Blood	6,250	0.057
			Serum	200	0.013
W.S.A.	27	Normal	Whole Blood	6,550	0.070
			Serum	50	0.012
C.G.C.	25	Normal	Whole Blood	6,450	0.09
			Serum	50	0.01
A.K.	60	Cancer of bladder	Whole Blood	20,550	0.088
		Bladder infection	Serum	50	0.016
J. R.*	34	Chronic Myeloid Leukemia	Whole Blood	128,000	8.00
			Serum	0	0.15
			Leukocyte- rich layer ‡	258,000	7.10
J.R.†	34	Chronic Myeloid Leukemia	Whole Blood	36,000	2.12
			Serum	100	0.10
			Leukocyte- rich layer ‡	109,500	5.55
W.C.G.	36	Chronic Myeloid Leukemia	Whole Blood	164,000	1.32
			Serum	150	0.066
			Leukocyte- rich layer ‡	320,000	3.57

KEY: \* before course of radiation.

† after course of radiation.

‡ from upper cellular layer of defibrinated blood after centrifuging.

EFFECT OF CLOTTING ON PARTITION OF HISTAMINE BETWEEN CELLULAR AND FLUID COMPONENTS OF HUMAN BLOOD. The data are summarized in Table 1. All histamine values are in gammas of histamine base per cubic centimeter of sample.

It is seen that in every instance only a very small fraction of the original cellular histamine has appeared in the serum after coagulation. The differential between whole blood and serum histamine is even more striking when

tion of histamine occurring as a result of coagulation of blood *per se.* and that important pharmacological activity due to histamine in serum obtained within 30 minutes of clotting under the conditions of these experiments does not exist. The presence of relatively enormous amounts of histamine in the white cell layer of centrifuged defibrinated leukemic blood supports the now generally accepted view that in man the majority of histamine is found in the myeloid leukocyte. Since clotting has

occurred, platelets cannot be said to be an important element in this white cell layer.

The failure to observe histamine release from cells to serum during coagulation does not support the concept that a proteolytic enzyme of the trypsin type is an important factor in coagulation of human blood. Trypsin and certain other proteolytic enzymes, it is now well established, have the ability to liberate histamine from cells.<sup>3,10,19,27</sup> The data do not exclude the possibility that some proteolytic enzyme not capable of producing histamine release is concerned in coagulation of human blood. Indeed they do not preclude that an amount of trypsin or trypsin-like enzyme large enough to play a rôle in coagulation was present, but that this was not in sufficient concentration to produce histamine release. These possible quantitative considerations must await further investigation. The relationship of the amount of trypsin necessary to promote coagulation on the one hand and to release histamine on the other may serve as a convenient clue to its presence or absence in the coagulation mechanism.

**STUDIES ON BLOOD HISTAMINE LEVELS IN HUMAN PATIENTS.** Survey determinations have been made on patients with the following syndromes or diseases: chronic and acute myelogenous leukemia, chronic lymphogenous leukemia, reticulum cell sarcoma, leukopenia of undetermined etiology, multiple myeloma, idiopathic thrombopenic purpura, Mikulicz syndrome, Raynaud's disease, idiopathic hypoprothrombinemia, trichinosis, pernicious anemia in relapse and after therapy, idiopathic non-thrombopenic purpura, carcinoma and infection of the bladder, Hodgkin's disease, Addison's disease, pneumococcal pneumonia, and macrocytic anemia with eosinophilia of undetermined etiology. In all instances total and differential leukocyte counts were made

at approximately the time blood was withdrawn for histamine studies. No attempt was made to investigate patients with allergic disease since reports are available on this group of individuals.<sup>17,22,23</sup>

While most normal individuals have blood histamine levels below .08 gamma histamine base per cc. of whole blood, we have considered only those patients with levels in excess of 0.10 gamma per cc. to have grossly abnormal values. By such a criterion, with the exception of patients with myeloid leukemia, only one individual studied had an abnormally high blood histamine level. This individual had a macrocytic anemia, leukocytosis of 23,600 per cu. mm. with eosinophilia, and the diagnosis was not clear. The blood histamine level in this instance was 0.18 gamma per cc. of whole blood. The patient ultimately died outside the hospital and no autopsy was performed.

It is clear that there is no close correlation between total or differential leukocyte count and the blood histamine. It was true in our series that individuals with very low numbers of granulocytes often had very low blood histamine values, but this is difficult to evaluate since normal subjects may also have markedly low histamine levels at times. However, while subjects with higher granulocyte counts tended to have somewhat higher histamine values, there was by no means a proportionate increase. Thus the blood histamine of a patient with carcinoma and infection of the bladder who had a total leukocyte count per cu. mm. of 20,500 with 80% granulocytes was 0.088 gamma per cc. The blood of a patient with 15,800 leukocytes per cu. mm. and 85% granulocytes contained but 0.05 gamma per cc., less than that of some normal subjects with normal counts. Nor was there close correlation found with any particular member of the granulocyte series. For example, one

patient with trichinosis and an absolute eosinophilia of 6300 per cu. mm. had a blood histamine level of but 0.03 gamma per cc. of blood while another individual with Hodgkin's disease and 5300 eosinophils per cu. mm. exhibited a level per cc. of 0.10 gamma. The patient with the elevated blood histamine of 0.18 gamma per cc. also had an absolute eosinophilia of 6500 per cu. mm. This lack of close correlation with total or differential leukocyte counts becomes even more apparent in patients with chronic myelogenous leukemia where histamine values of tremendous magnitude were obtained. Table 2 shows the findings in this group.

in numbers of cells cannot explain the tremendous amount of blood histamine in some cases of myelogenous leukemia. Thus, computing from normal values, the total cell count in J. R. and in F. T. cannot adequately explain the marked increase above normal of the blood histamine. The individual cells must contain much more histamine than normal cells, but whether this is limited to certain stages of cell development or is a general phenomenon cannot be ascertained from our data.

It is interesting to speculate on the significance of the histamine content of the myeloid leukocyte both in normal individuals and in patients with myelogenous leukemia. Little is known of the

TABLE 2 — TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS AND BLOOD HISTAMINE VALUES IN HUMAN SUBJECTS WITH CHRONIC MYELOGINOUS LEUKEMIA

Patient	Date	Total WBC						Histamine base						
		per cu. mm.	Bas.	Eos.	Blast	Myelo.	Juv.	Stabs.	Seg.	Lymphs.	Monos.	Other	cc, whole blood	
W.C.G.°	7-2-46	199,500	2.5	2.0	0.5	21.5	17.0	33.0	33.0	2.0	0.0	1.0	2.5	
W.C.G.°	10-21-46	164,000	2.0	1.0	0.0	18.0	13.5	28.0	35.0	2.0	0.0	0.5	1.32	
J.R.° before x-ray	9-17-46	128,000	5.5	2.0	2.0	18.0	21.5	32.5	14.0	3.5	0.0	1.0	8.0	
J.R.° after x-ray	9-30-46	36,000	2.0	2.5	0.0	13.5								
F.T.	11-12-46	177,000	2.5	4.0	1.0	24.5	5.5	26.0	43.5	4.5	0.0	2.5	2.12	
° Same							14.0	30.0	31.5	2.0	0.0	0.5	3.75	

It is readily apparent that differences in differential cell types or total leukocyte counts do not permit any conclusions as to which members of the granulocyte series are richest in histamine content. It is of interest that the blood histamine level of J. R. fell almost proportionately with the leukocyte count after roentgen radiation therapy. In addition to the above, one patient with acute myelogenous leukemia was studied. The total leukocyte count was only 9700 per cu. mm. with 12% blast cells. The blood histamine level was 0.10 gamma per cc. of blood—at upper limits of normal or perhaps slightly above. In a single case of chronic lymphatic leukemia with 475,000 cells per cu. mm. the blood histamine was low—0.025 gamma per cc. of whole blood.

It is also apparent that mere increase

physiologic functions, if any, of histamine within the body. However, there is probably sufficient histamine within the myeloid leukocytes of many normal individuals to produce significant effects if any large portion of it were suddenly liberated.<sup>14</sup> In anaphylactic reactions histamine liberated from blood cells may be added to that liberated from other tissues. The extremely large amounts of blood histamine found in patients with myelogenous leukemia, if liberated rapidly, could most certainly result in profound clinical symptoms. In view of the probability that there is a rapid turnover of leukemic leukocytes within the body, one can but wonder what effect the liberation of histamine may have on the economy of these patients. In the case of normal individuals with localized pyogenic infection it is

possible that the cardinal signs of inflammation may be partly due to the breakdown of large numbers of myeloid leukocytes with local liberation of histamine. Certainly, the so-called "cold abscess" in which the non-histamine containing mononuclear is the predominant cell type involved presents far different clinical manifestations than the pyogenic abscess with its predominantly granulocytic exudate.

**Summary.** Data are presented on the partition of blood histamine before and after clotting and on the correlation of blood histamine levels with the blood leukocyte picture in health and disease

states. The data support the now generally accepted view that most of the blood histamine in man is found in the myeloid leukocyte. They show that there is little if any transfer of histamine from cells to serum when human blood is allowed to clot. Tremendous elevations in blood histamine were found in patients with chronic myelogenous leukemia, but no close correlation was obtained between the level of blood histamine and the total or differential leukocyte count. The possible significance of the presence of appreciable amounts of histamine within the myeloid leukocyte is discussed.

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# THE INTERRELATIONSHIP OF HODGKIN'S DISEASE AND OTHER LYMPHATIC TUMORS†

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THE cellular structure of lymphatic tumors is extremely labile, and transition from one apparently distinct type to another is frequently observed. This is not surprising, when one appreciates that all cellular components of lymphatic tissue are derived from the same mesenchymal stem cells. Attempts to subdivide these interrelated tumors on the basis of rigid histologic criteria have resulted in a confused nomenclature which serves only to cloud the facts. Radiologists and clinicians, even many experienced pathologists, prefer to regard the subgroups as separate neoplastic entities. Thus, a differential diagnosis between Hodgkin's disease and reticulum cell sarcoma, or between lymphosarcoma and chronic lymphatic leukemia, would seem to make a great deal of difference; actually it makes little or none. They are all malignant mesenchymal tumors which vary only in degree and type of differentiation.

The views that we are presenting are not new. As early as 1906 Gibbons regarded Hodgkin's disease as a variant of lymphosarcoma, and the following year Coley suggested that the term

"Hodgkin's disease" be dropped in favor of "lymphosarcomatosis." Ginsburg (1934) came to the conclusion that "biologically, Hodgkin's disease varies in no fundamental characteristic from lymphosarcoma. Whatever variations it may present at times are merely variations that one would expect to find in any disease affecting different individuals under different constitutional and environmental conditions."

In 1913 Oliver added "endothelioma" (reticulum cell sarcoma) to the group, and Warren and Picena (1941) clearly demonstrated the steps which linked reticulum cell sarcoma with lymphosarcoma, although they omitted Hodgkin's disease which they considered "a more complicated process and still controversial." Earlier, however, Callender (1934) implied that reticulum cell sarcoma and the sarcomatous form of Hodgkin's disease were closely allied. The relationship between Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma, was shown by Herbut, Miller, and Erf (1945), who described 6 cases "that at one time during the lives of the patients were diagnosed Hodgkin's disease and at another time

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as lymphosarcoma, and that at autopsy showed various combinations of Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma." They considered "the three diseases as arising from a common stem cell—the reticulum cell—and then differentiating in one direction or another according to the amount and type of stimulation."

Mallory (1914) proposed the term "malignant lymphoblastoma" to include lymphosarcoma, lymphatic leukemia, and Hodgkin's disease; two years later Warfield and Kristjanson described a case which featured all three of these variants, a patient with a typical lymphosarcoma in whom a lymphatic leukemic blood picture developed and whose axillary lymph nodes, removed shortly before death, presented the histologic appearances of Hodgkin's disease. Richter (1928) observed a case of "generalized reticular cell sarcoma of lymph nodes associated with lymphatic leukemia," while Gittins and Hawksley (1933) reported the coexistence in a child of reticulum cell sarcoma and monocytic leukemia.

Warthin (1931) stated "that Hodgkin's disease is a neoplasm and related genetically to the lymphoblastomas, of which both the aleukemic and leukemic forms are identical pathologically; and that mycosis fungoides is likewise a neoplasm belonging to the same generic group. The essential difference between these different clinical forms consists in different degrees of dedifferentiation and entdifferntiation, and the organ or tissue primarily involved. Transition forms exist between all of these groups, and one type may be transformed into another." Warthin's inclusion of mycosis fungoides in the group was supported by the papers of Wile and Stiles (1935) and MacCormac (1941), each of which contained the description of a mutation from this condition to Hodgkin's disease.

We found only one reference to

fibrosarcoma as an associated variant among the lymphomas, a situation that we encountered 8 times in our series. Fraser and Meokie (1933) described their Case 10 as having had a biopsy performed which was typical of Hodgkin's disease. At autopsy "in some parts the histological appearances were unequivocally those of Hodgkin's disease, but in other parts the tissue was almost wholly composed of immature fibroblasts, with here and there a distorted though plainly recognizable Dorothy Reed cell."

The most labile of all lymphatic tumors is the follicular lymphoblastoma which rarely retains its identity throughout the course of the disease, but at some unpredictable time undergoes transition to lymphosarcoma, reticulum cell sarcoma, lymphatic leukemia, Hodgkin's disease, or combinations thereof. Symmers (1938) (1941) (1942) (1948) described such transformations. Recently, under the title "Manifold Manifestations of Reticulo-Endothelial Disease," Tedeschi and Carnicelli reported a case showing first a "cervical granuloma which disclosed the characteristic pattern of Hodgkin's disease; then acute hemolytic anemia, which successfully responded to splenectomy, and last a recurrence of the cervical granuloma in association with giant follicular lymphadenopathy."

Material. For some years we have been aware of the fluidity existing among tumors of lymphatic tissue. An assignment to examine and render a report on all lymphatic and hemopoietic tissues submitted to the Army Institute of Pathology during the recent war offered a unique opportunity to study this problem in detail. The number of cases was statistically significant, and in many the course of the disease could be followed through the medium of one or more biopsies to the autopsy. Records in most instances were good, and the tissue samples adequate.

The study was centered principally around Hodgkin's disease. Any case in which this diagnosis was not completely acceptable on the basis of either biopsy or autopsy specimens was discarded. The final *Hodgkin's material*, comprised 700 cases as follows:

Autopsy Series:	Cases
With no biopsy	62
With 1 biopsy	113
With 2 biopsies	21
With 3 biopsies	4
	200
Biopsy Series:	
One biopsy	431
Two biopsies	60
Three biopsies	9
	500

The serial biopsies served to augment the biopsy-autopsy material in the study of transitions from one variant to another, while the single biopsies proved valuable in determining the incidence of several histologic patterns in the same lymph node.

An additional series of 600 cases contained *lymphomas apart from Hodgkin's disease* (follicular lymphoblastoma, lymphosarcoma, reticulum cell sarcoma, lymphatic leukemia, monocytic leukemia). This group included cases displaying transitions and combinations among themselves, and furnished data with which to complete our scheme of interrelationship (Fig. 1).

Careful note was made of treatment given the patients, especially with radiant energy. A significantly large group had received no treatment and could be used as a control. Radiotherapy apparently had no influence either in initiating or deterring transitions. Naturally occurring fibrosis sometimes exceeded that observed in heavily irradiated patients, and little or no fibrous reaction was apparent in the tumors of others who had received large doses of Roentgen-rays.

**TERMINOLOGY AND HISTOLOGIC CRITERIA.** We grouped our cases of *Hodgkin's disease* according to the histologic classification of Jackson and Parker (paragranuloma, granuloma, sarcoma) on the basis of the predominating microscopic pattern, even though the picture was a mixed one in many instances. Thus we could include considerable changes in cellular structure within this single disease category.

*Hodgkin's paragranuloma* is characterized by a partially to completely effaced nodal pattern, with small lymphocytes predominating, along with a scattering of plasmacytes, reticulum cells, and Reed-Sternberg cells (Plates

1B, 2A, 3A, 8A). *Hodgkin's granuloma* is the oldtime textbook picture that needs no further elaboration (Plates 1B, 2B & D, 3B, 4D, 5A, 6A, 7A, 10B & C).

We did not find any fundamental difference between *Hodgkin's sarcoma* and *reticulum cell sarcoma*, and consequently used the terms synonymously in our scheme (Fig. 1), irrespective of the fortuitous occurrence of tumor giant cells that could be regarded as Reed-Sternberg cells. Both reticulum cell and Hodgkin's sarcoma showed variants from an anaplastic, syncytial pattern to a well differentiated reticulum cell structure (Plates 1E, 2D, 3C & D, 5B & C, 6B, 7B, 8D, 10A, 11D).

*Follicular lymphoblastoma* is a lymphatic tumor, localized or multicentric, in which there is differentiation to follicles, to be distinguished from reactive hyperplasia of follicles, though sometimes with difficulty. Striking numerical (not necessarily dimensional) increase in follicles, distortion of nodal pattern, and absence of phagocytosis within follicular centers serve to distinguish the tumor (Plates 1A, 11B).

*Lymphosarcoma* denotes tumors made up of relatively uniform round cells which may be small, well differentiated lymphocytes (lymphocytoma) or large, anaplastic lymphocytes (lymphoblastoma) (Plate 8C & E, 11C).

*Lymphatic leukemia* differs only in being a more generalized neoplasia without striking local tumefaction, with or without the appearance of lymphoid cells in the circulating blood (Plate 11A & C). The same relationship exists between *monocytic leukemia* and *reticulum cell sarcoma* as regards the type of proliferating cell.

These terms are useful, but only to designate the predominating histologic pattern of a lymphoma at the time of a particular examination of tissue and blood.



PLATE 1.—White female, 33. Duration 23 months. Radiotherapy 7600 r.

- A. 1st biopsy (lymph node): Follicular lymphoblastoma; large, closely packed lymphoid nodules uniformly distributed throughout the node (X32).
  - B. 2nd biopsy (lymph node): Hodgkin's paraganuloma; small lymphocytes predominate; a Reed-Sternberg cell is seen in the center (X600).
  - C. 3rd biopsy (lymph node): Hodgkin's granuloma; the dark smudgy cells are eosinophilic and the large central cell a Reed-Sternberg form (X600).
  - D. Autopsy (lymph node): A sarcomatous proliferation of fibroblasts entirely replacing nodal parenchyma (X600).
  - E. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma, the predominating picture in lesions found at autopsy (X600).
- (A.I.P. Acc. 135516. Neg. Nos. 94710, 93009, -008, -012, -018.)

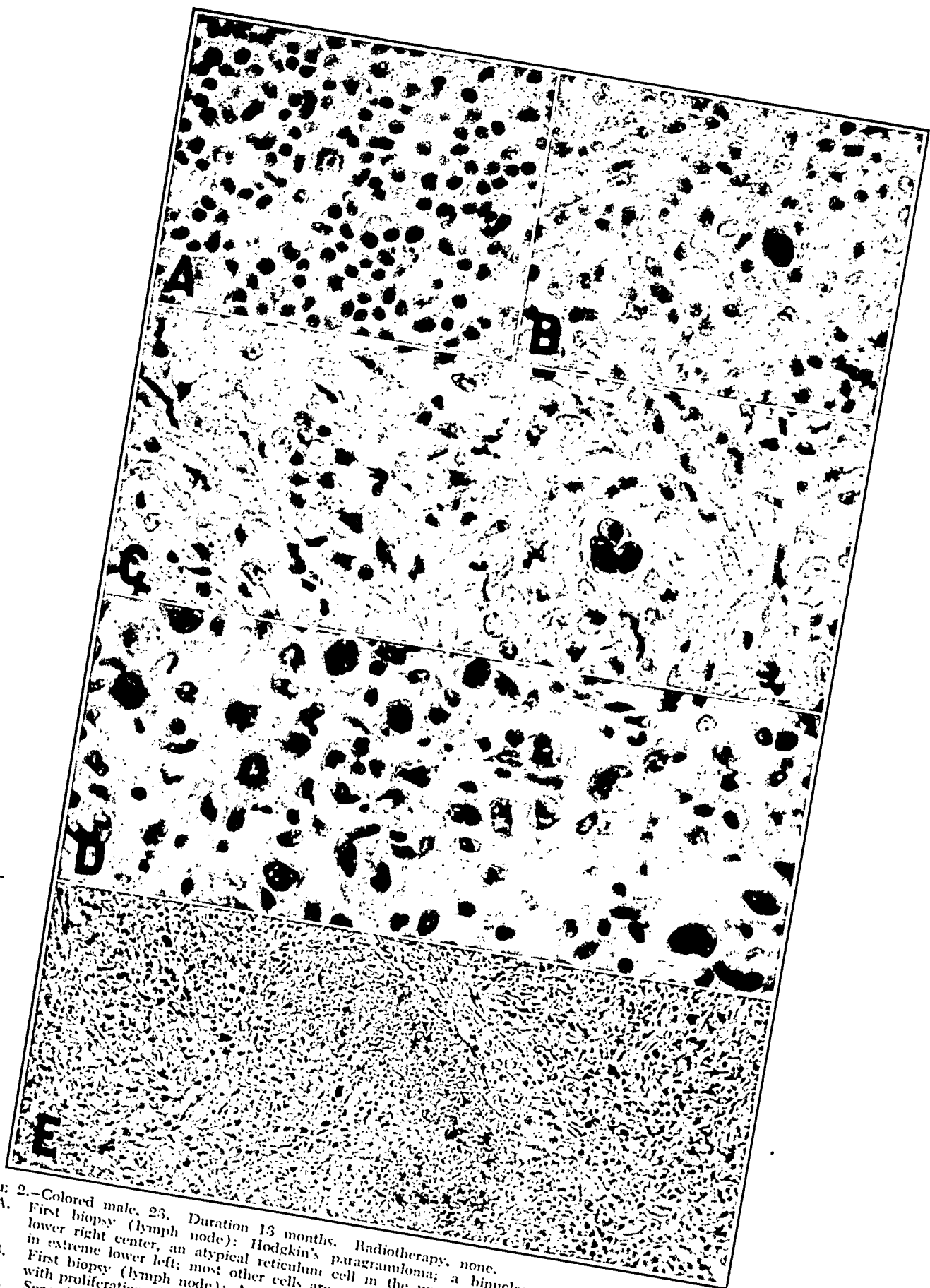


PLATE 2.—Colored male, 23. Duration 13 months. Radiotherapy, none.

A. First biopsy (lymph node): Hodgkin's paragranuloma; a binuclear plasmacyte is seen in the lower right center, an atypical reticulum cell in the upper left center, and a Reed-Sternberg cell in extreme lower left; most other cells are small lymphocytes (X600).

B. First biopsy (lymph node): A small area of same node as A acquiring granulomatous characters, with proliferation of reticulum cells and fibroblasts (X600).

C. Second biopsy (lymph node): Hodgkin's granuloma with marked fibrosis (X600).

D. Autopsy (lymph node): Hodgkin's granuloma with marked fibrosis (X600).

E. Autopsy (spleen): Hodgkin's granuloma; very little sarcomatous change was evident in the richly distributed splenic lesions; some granulomatous foci also persisted in the liver (X150). (A.I.P. Acc. 118663, Neg. Nos. 95018, -019, -020, -021, -022.)

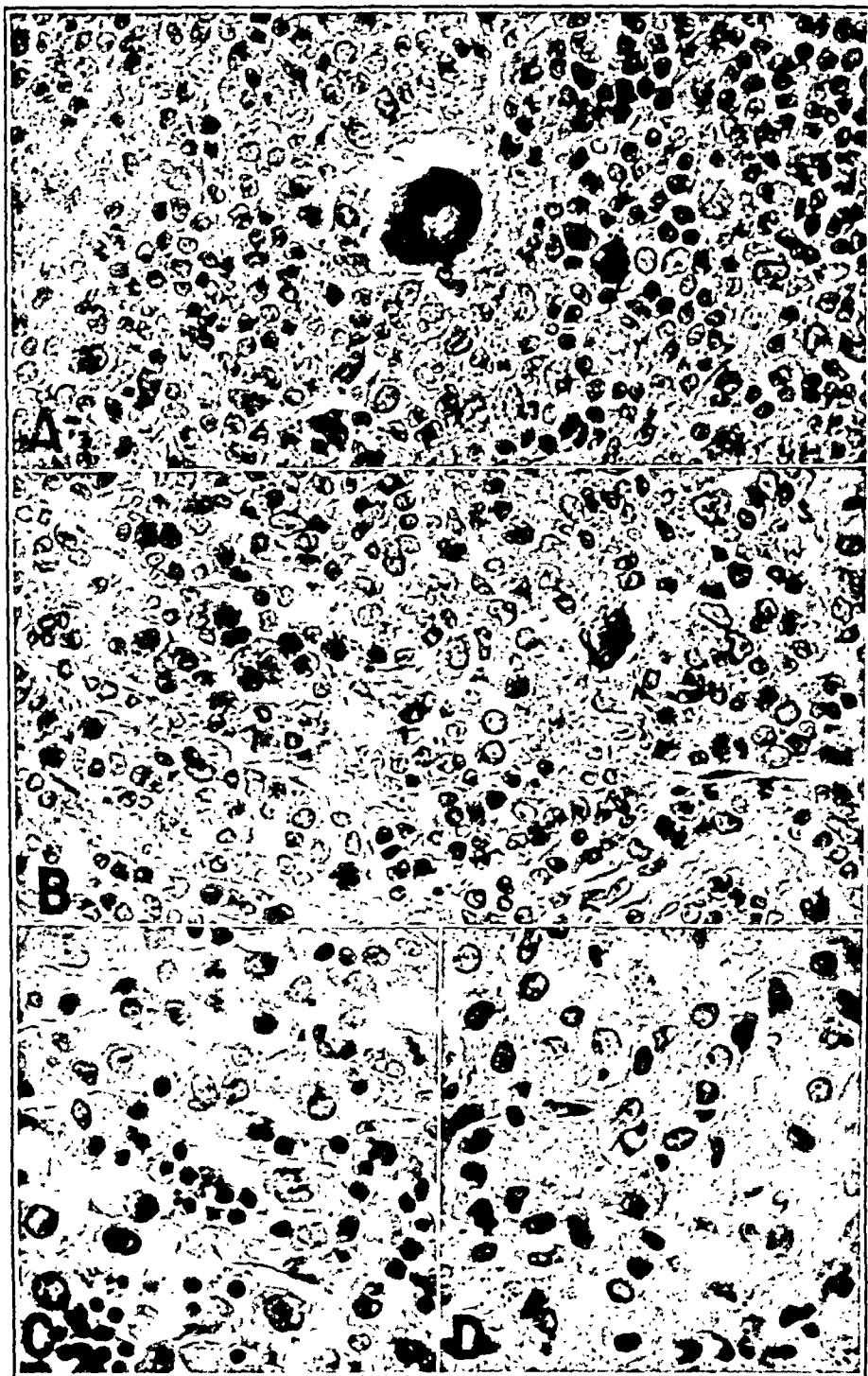


PLATE 3.—White male, 35. Duration 10 months. Radiotherapy, not stated.

- A. 1st biopsy (lymph node): Hodgkin's paraganuloma; proliferation of reticulum cells and a few fibroblasts among the lymphocytes heralds a transition to the granulomatous form; the Reed-Sternberg cell in the center is extraordinarily large (X600).
- B. 2nd biopsy (lymph node): Hodgkin's granuloma, most of the lymphocytes have disappeared, and a pronounced eosinophilia is present (X600).
- C. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma showing an admixture of large reticulum cell and small lymphocyte components (X600).
- D. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma, with a virtually pure reticulum cell proliferation (X600).

(continued on Plate 4)

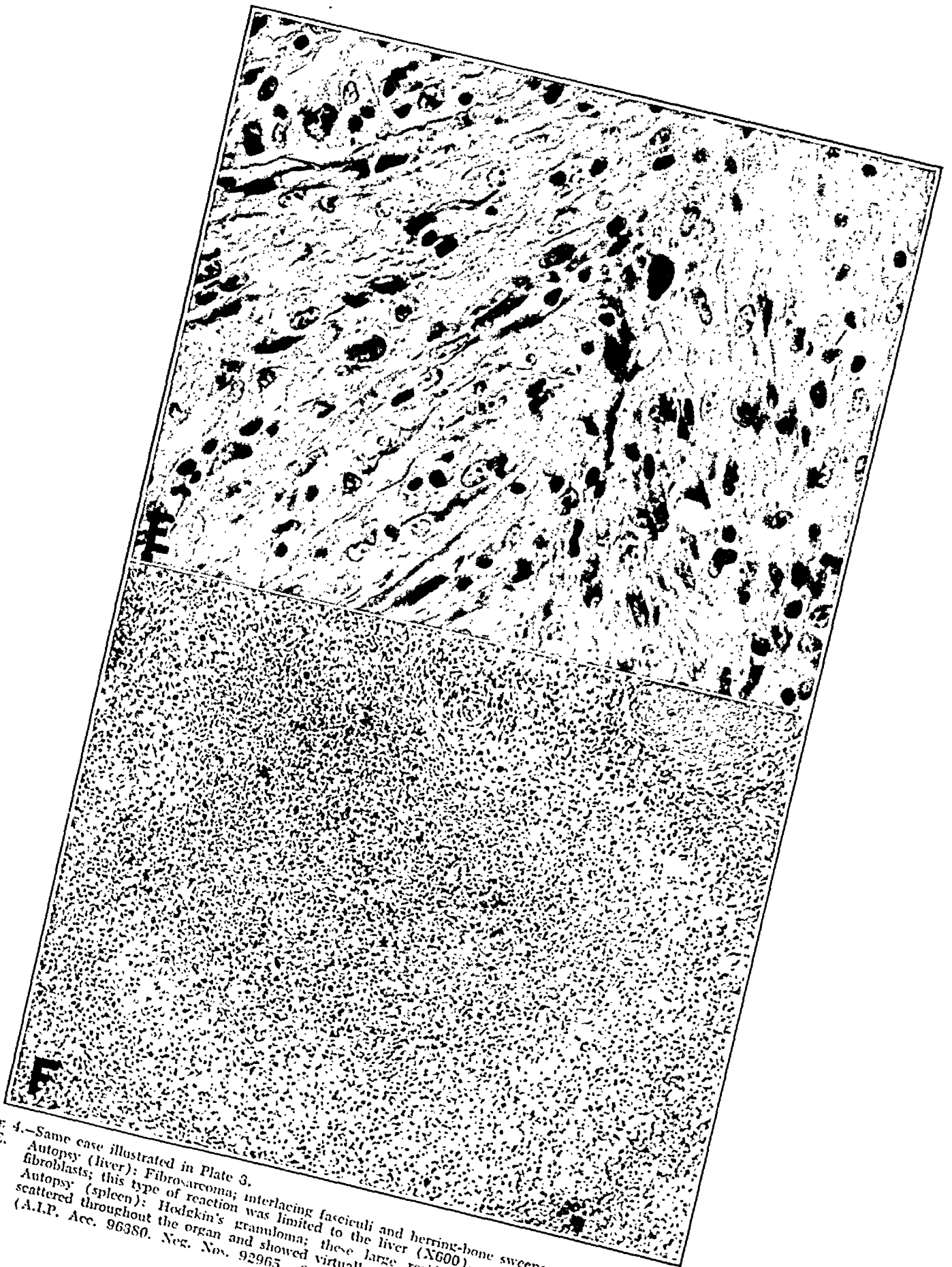


PLATE 4.—Same case illustrated in Plate 3.  
 E. Autopsy (liver): Fibrosarcoma; interlacing fasciculi and herring-bone sweeps of obviously neoplastic fibroblasts; this type of reaction was limited to the liver (X600).  
 F. Autopsy (spleen): Hodgkin's granuloma; these large residual granulomatous foci were widely scattered throughout the organ and showed virtually no sarcomatous change (X170).  
 (A.I.P. Acc. 96380. Neg. Nos. 92965, -966, -969, -970, -972, -973.)

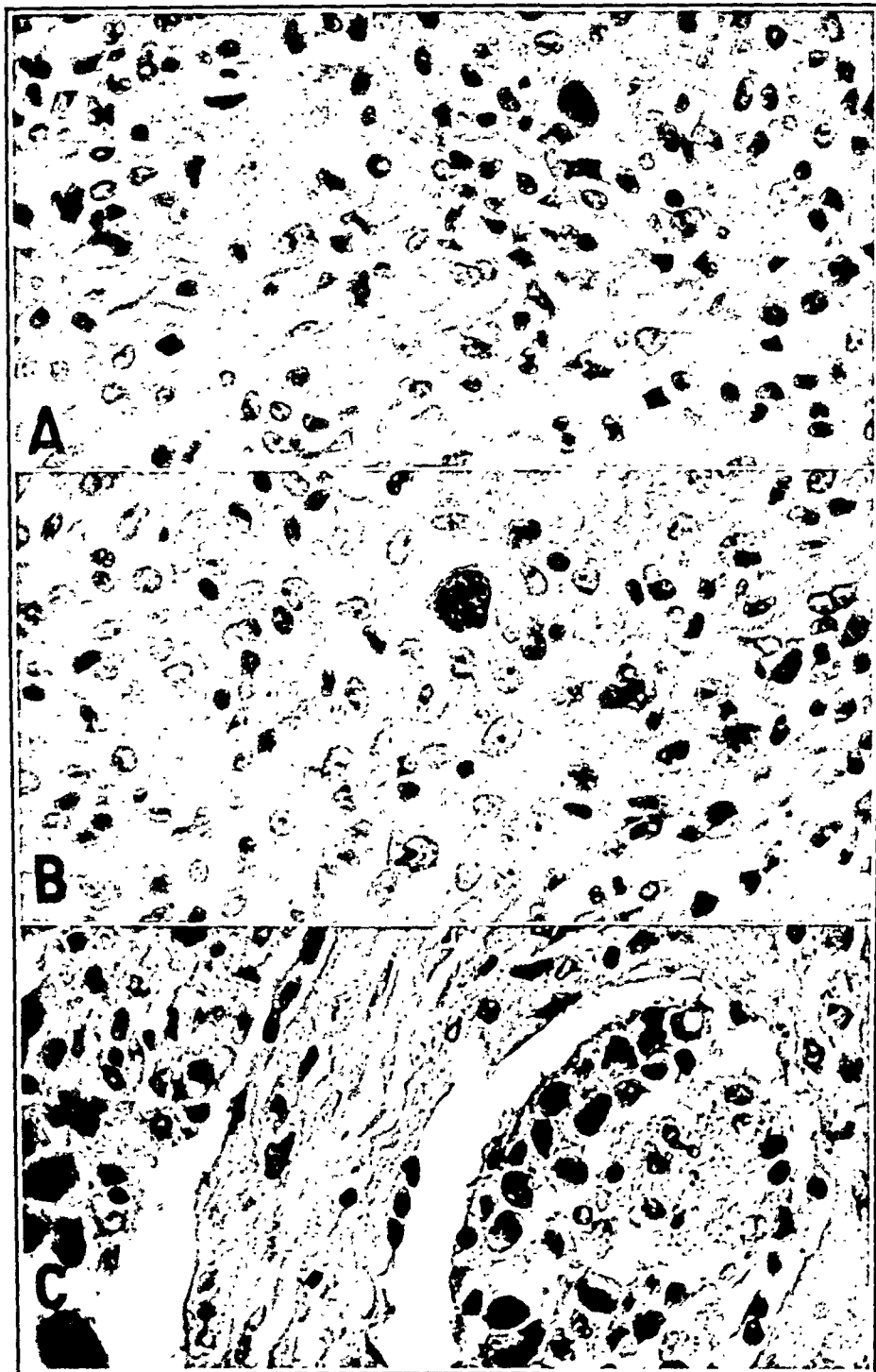


PLATE 5. White male, 29. Duration 5½ months. Radiotherapy 12,800 r.

- A. 1st biopsy (lymph node): Hodgkin's granuloma; collagen deposit throughout the node is abundant (X600).
- B. 2nd biopsy (lymph node): Stage of transition between Hodgkin's granuloma and sarcoma (X600).
- C. Autopsy (perinodal tissue): Hodgkin's (reticulum cell) sarcoma; all granulomatous features have disappeared, and the tumor shows extensive invasion and metastasis via vascular pathways (X600). (A.L.P. Acc. 150157, Neg. Nos. 93023, -024, -025.)

**Observations.** Cases of Hodgkin's disease were divided according to the to the Jackson-Parker classification as in table below.

In Fig. 1 the arrows leading to and from the Hodgkin's disease rectangle, and those contained within it, indicate the transitions actually observed in this series, the heavy lines showing the most common changes and the double-headed arrows the to-and-fro shifts.

A virtually complete alteration in the histologic pattern of the tumor was noted in 39% of the 138 autopsied cases in which biopsies were available, and in

31% of the serial biopsy group (Table 1). Still more striking was the incidence of pure type tumors in only 19 and 23% respectively in these two groups. When only one observation was possible, either of autopsy or biopsy material, unmixed pictures were found in the majority of cases (74 and 71%); this may have represented either an early phase before transition was initiated, or a late one after the pattern was finally established.

Major transitions are listed in Table 2. In both the biopsy-autopsy and sequential biopsy series the most fre-

	Autopsy Series		Biopsy Series		Total	
	No.	%	No.	%	No.	%
Hodgkin's paraganuloma	7	3.5	93	18.6	100	14.3
Hodgkin's granuloma	120	60.	378	75.6	498	71.1
Hodgkin's sarcoma	73	36.5	29	5.8	102	14.6
Total	200		500		700	

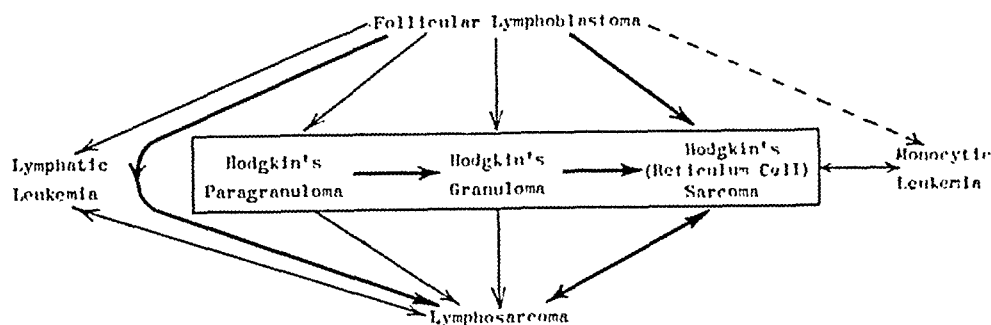


FIG. 1.—This diagram represents transitions actually observed between the several variants of malignant lymphoma, and is not to be construed as indicating genetic sequences. The heavy lines show transitions most frequently found, the lighter lines the uncommon ones. Double-headed arrows signify a change in either direction. The dotted line implies a possible sequence not encountered in our series. Associated fibrosarcomas are not shown here.

TABLE 1.—TRANSITIONS AND COMBINATIONS OF HISTOLOGIC TYPES.

	With Transition		Without Transition		Pure Type		Combined Types		Cases	
	No.	%	No.	%	No.	%	No.	%		
Autopsy Series (200 cases)										
With Biopsy	54	39	84	61	26	19	112	81	135	
Without Biopsy	--	--	--	--	45	74	17	26	62	
Biopsy Series (500 cases)										
Sequential Biopsies	21	31	48	69	16	23	53	77	69	
Single Biopsy	--	--	--	--	305	71	126	29	431	



TABLE 2.—VARIETIES OF MAJOR TRANSITIONS OBSERVED.

	Initial Type	Terminal Type	Cases
Autopsy Series with Biopsy:	Hodgkin's paraganuloma	Hodgkin's granuloma	7
	Hodgkin's paraganuloma	Hodgkin's sarcoma	6 (†)
	Hodgkin's granuloma	Hodgkin's sarcoma	28
	Hodgkin's granuloma	Fibrosarcoma	1
	Hodgkin's sarcoma	Hodgkin's paraganuloma	2 (?) (°)
	Hodgkin's sarcoma	Hodgkin's granuloma	8 (?) (°)
Sequential Biopsy Series:	Follicular lymphoblastoma	Hodgkin's granuloma	1
	Follicular lymphoblastoma	Hodgkin's sarcoma	1
	Hodgkin's paraganuloma	Hodgkin's granuloma	7
	Hodgkin's granuloma	Hodgkin's paraganuloma	1 (?) (°)
	Hodgkin's granuloma	Hodgkin's sarcoma	9
	Hodgkin's sarcoma	Hodgkin's granuloma	2 (?) (°)
	Follicular lymphoblastoma	Hodgkin's paraganuloma	1
	Follicular lymphoblastoma	Hodgkin's sarcoma	1

(†) One of these was a combination of Hodgkin's (reticulum cell) sarcoma and lymphosarcoma, the two types being distinct in separate foci.

(°) It is not clear whether these cases show a reverse transition toward better differentiation, or whether the biopsy merely disclosed a local variant of the major type of lesion observed at autopsy.

TABLE 3.

TYPE LESIONS OBSERVED IN DIFFERENT LYMPH NODES OR ORGANS OF THE SAME INDIVIDUAL AT AUTOPSY (129 cases)											
Hodgkin's paraganuloma		X	X			X	X	X			
Hodgkin's granuloma	X	X	X	X	X				X		
Hodgkin's sarcoma	X		X	X	X	X	X	X	X	X	
Lymphosarcoma					X	X					
Fibrosarcoma				X							
Follicular lymphoblastoma								X	X	X	
Number of cases	90	13	13	4	3	2	1	1	1	1	
COMBINATIONS OF TYPE LESIONS(*) OBSERVED IN SINGLE LYMPH NODES (255 cases)											
Hodgkin's paraganuloma		X	X	X				X		X	
Hodgkin's granuloma	X	X			X	X	X	X	X		X
Hodgkin's sarcoma	X			X			X	X	X	X	X
Lymphosarcoma					X				X		
Fibrosarcoma						X	X				
Follicular lymphoblastoma			X							X	X
Number of cases	132	101	7	4	2	2	2	1	1	1	1

(\*) Histologic patterns of significantly large fields which, if viewed alone, would justify the diagnoses as listed.

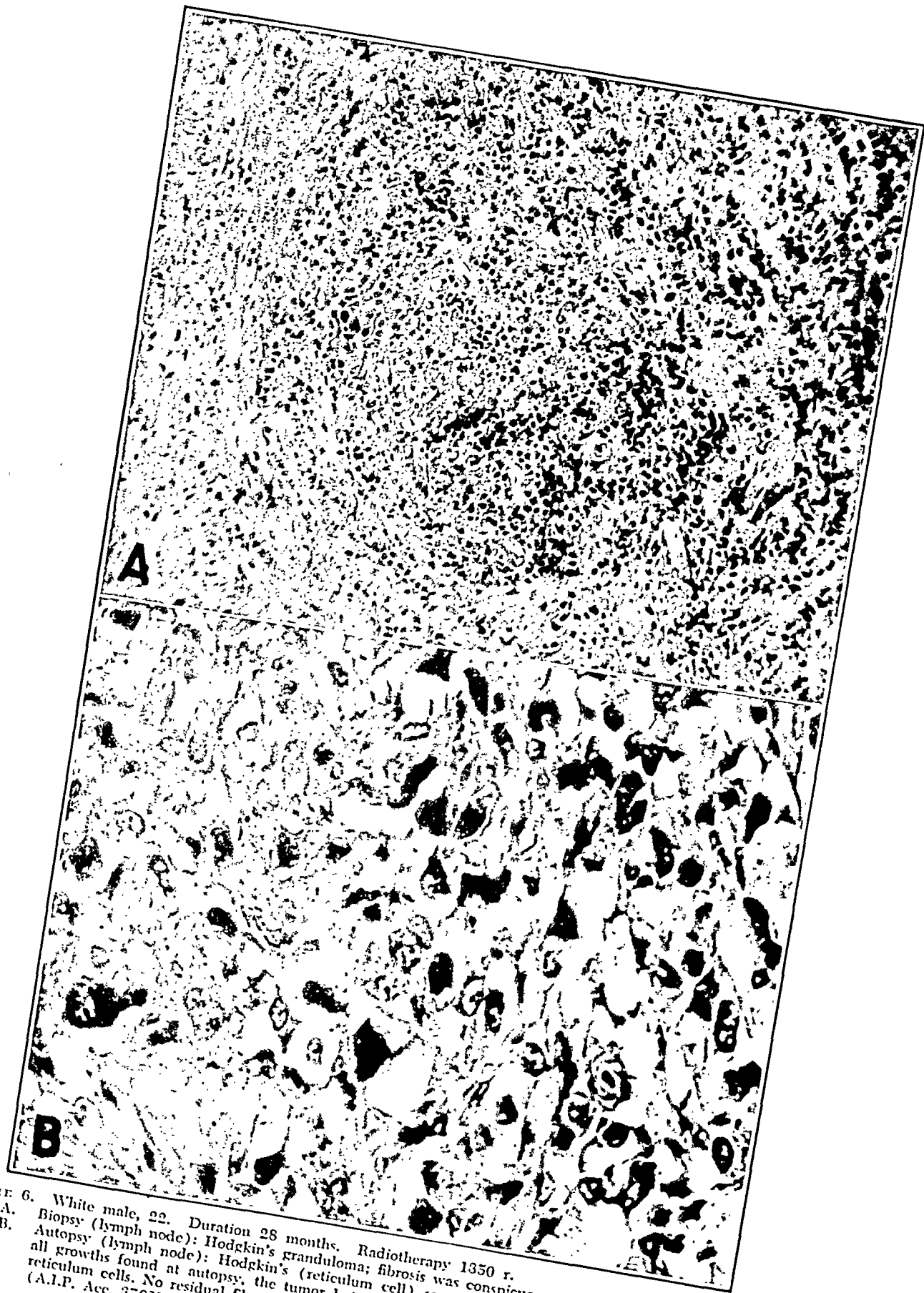


PLATE 6. White male, 22. Duration 28 months. Radiotherapy 1350 r.  
 A. Biopsy (lymph node): Hodgkin's granuloma; fibrosis was conspicuous prior to irradiation (X190).  
 B. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma; the area shown is representative of all growths found at autopsy, the tumor being composed of moderately well differentiated stellate reticulum cells. No residual fibrosis was evident (X750).  
 (A.I.P. Acc. 37635. Neg. Nos. 94672, -693.)



PLATE 7. White male, 22. Duration 4 months. Radiotherapy, none.

- A. Biopsy (lymph node): Hodgkin's granuloma, characterized by a multiplicity of cell types, including many eosinophils (X600).
- B. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma; an unusual variant with huge tumor cells, all the more striking by comparison with A, photographed at the same magnification (X600). (A.L.P. Acc. 104376. Neg. Nos. 92993, -994.)

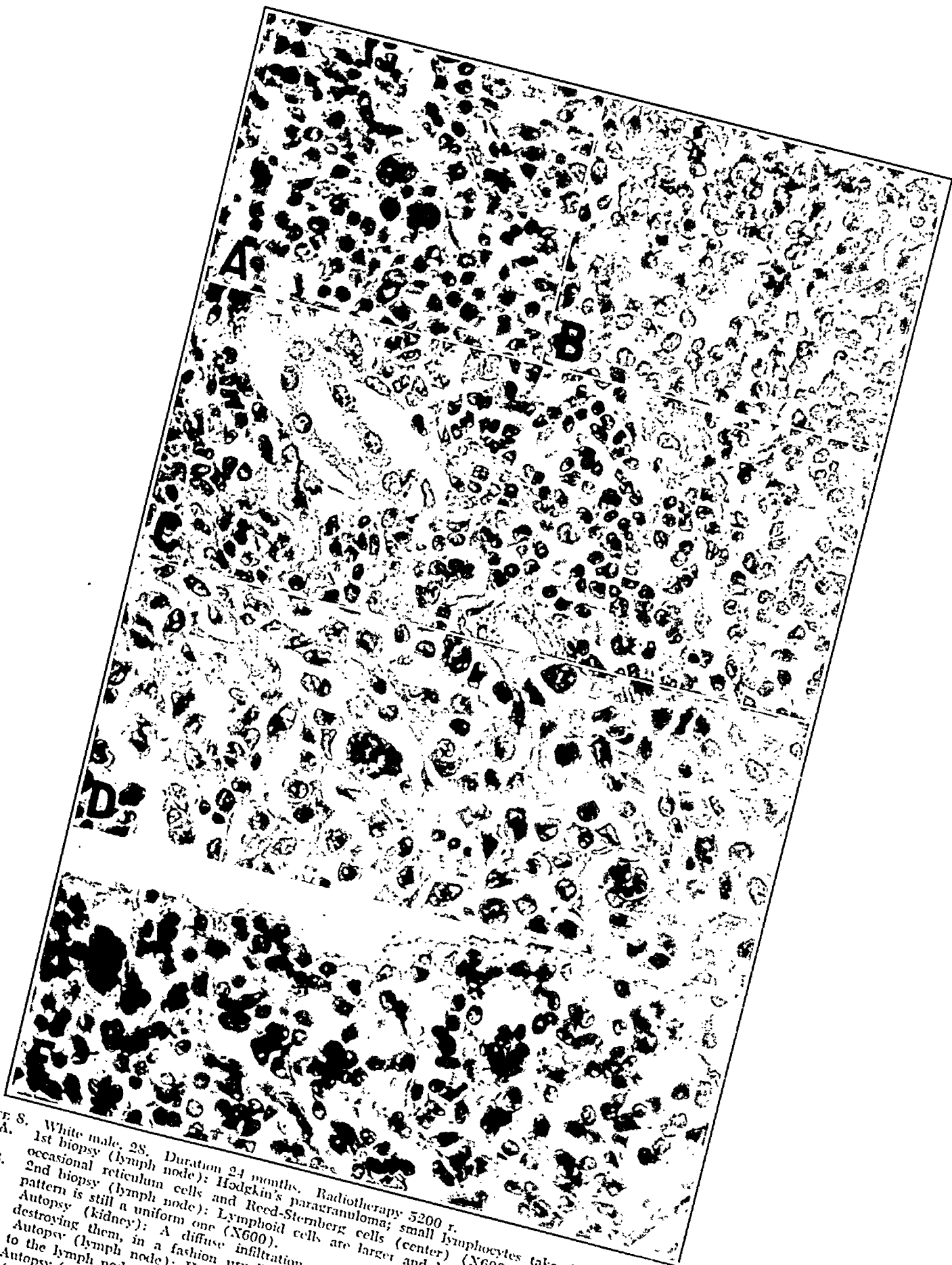


PLATE 8. White male, 28. Duration 24 months. Radiotherapy 5200 r.  
 A. 1st biopsy (lymph node): Hodgkin's paracrystalloma; small lymphocytes take the foreground, with occasional reticulum cells and Reed-Sternberg cells (center) (X600).  
 B. 2nd biopsy (lymph node): Lymphoid cells are larger and have vesicular nuclei, but the general pattern is still a uniform one (X600).  
 C. Autopsy (kidney): A diffuse infiltration of small lymphocytes spreads tubules apart without destroying them, in a fashion usually found in lymphatic leukemia (X600).  
 D. Autopsy (lymph node): Hodgkin's (reticulum cell) sarcoma; this multifocal pattern was limited to the lymph nodes (X600).  
 E. Autopsy (meninges): This uniform small lymphocyte infiltration resembles that in the kidneys (X600). (A.I.P. Acc. 125695. Neg. Nos. 93029, -030, -031, -032, -034.)

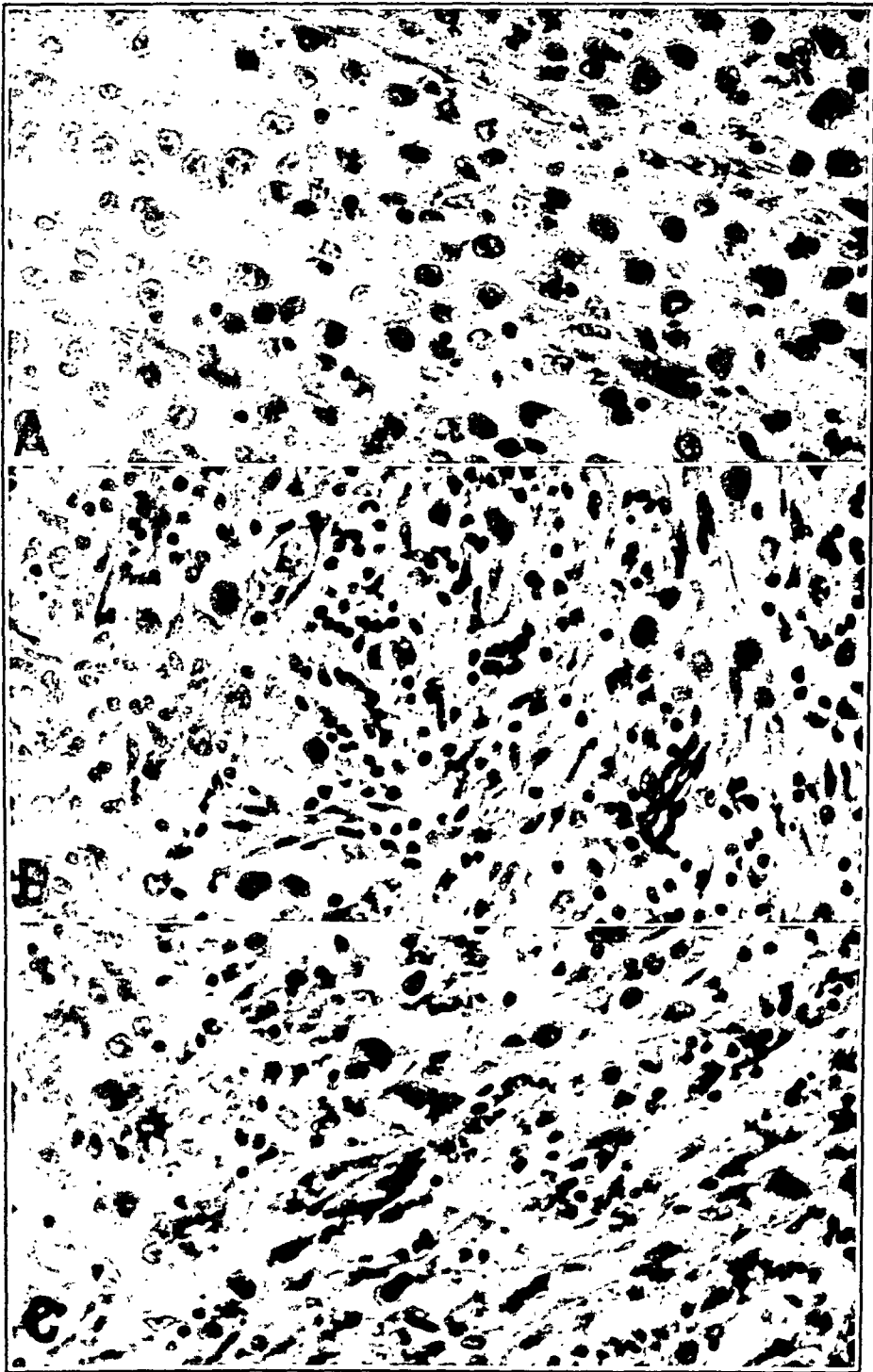


PLATE 9. White male, 23. Duration 3 months. Radiotherapy, none.  
3 areas from the original lymph node biopsy.

- A. 1st area: Tumor composed of fairly uniform lymphoid cells which are large and have vesicular nuclei with nucleoli (lymphosarcoma, lymphoblastic type) (X600).
- B. 2nd area: Granulomatous pattern with sparse sprinkling of lymphoblastic tumor cells (X600).
- C. 3rd area: Granulomatous pattern, but with predominance of angioblasts and new capillary formation (X600).

(A.I.P. No. 133540. Neg. Nos. 92988, -989, -990.)

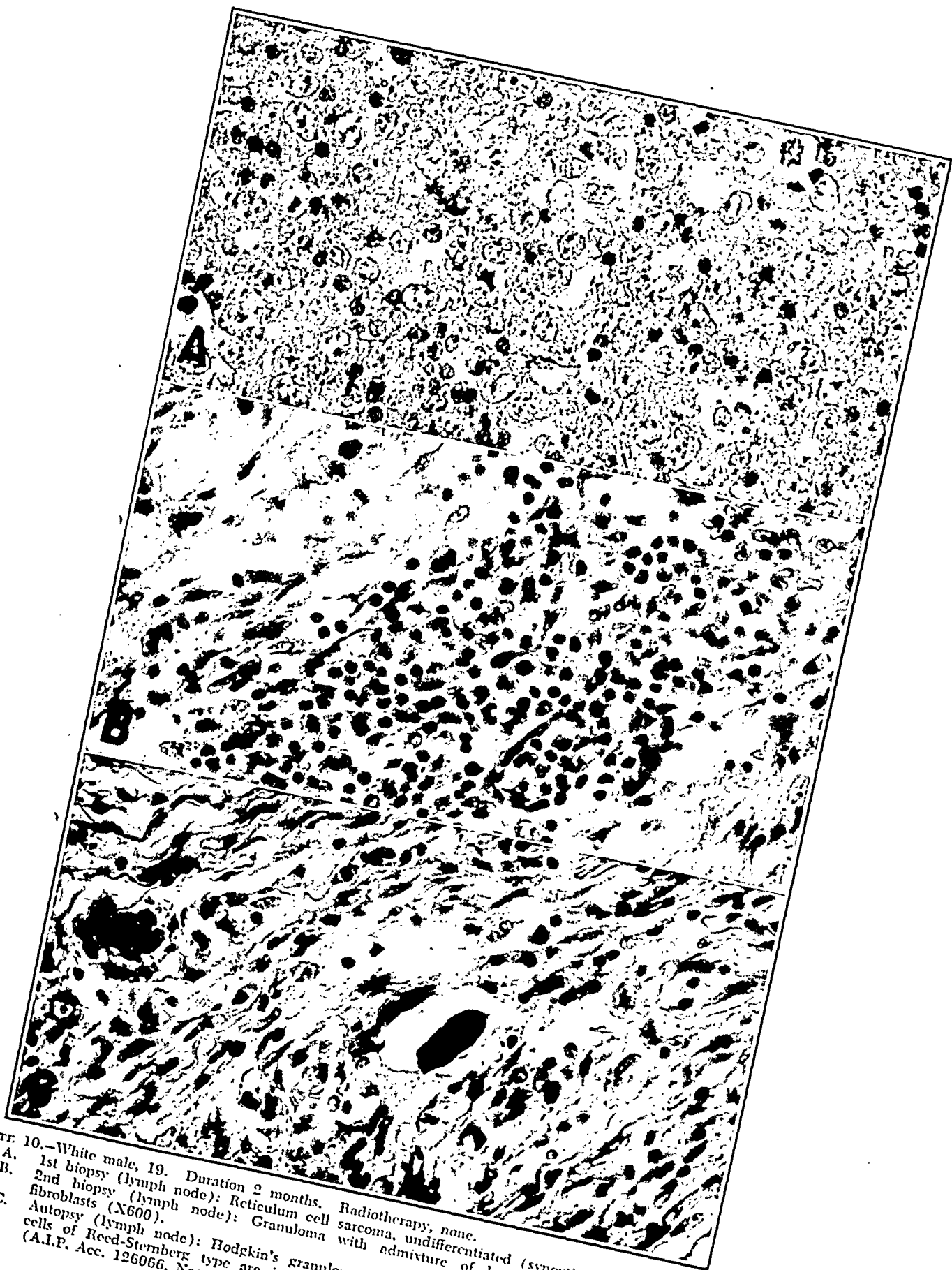


PLATE 10.—White male, 19. Duration 2 months. Radiotherapy, none.  
 A. 1st biopsy (lymph node): Reticulum cell sarcoma, undifferentiated (syncytial) type (X600).  
 B. 2nd biopsy (lymph node): Granuloma with admixture of lymphocytes, reticulum cells, and fibroblasts (X600).  
 C. Autopsy (lymph node): Hodgkin's granuloma; fibrosis is more pronounced, and smudged giant cells of Reed-Sternberg type are interspersed (X600).  
 (A.I.P. Acc. 126066. Neg. Nos. 93005, -006, 007.)

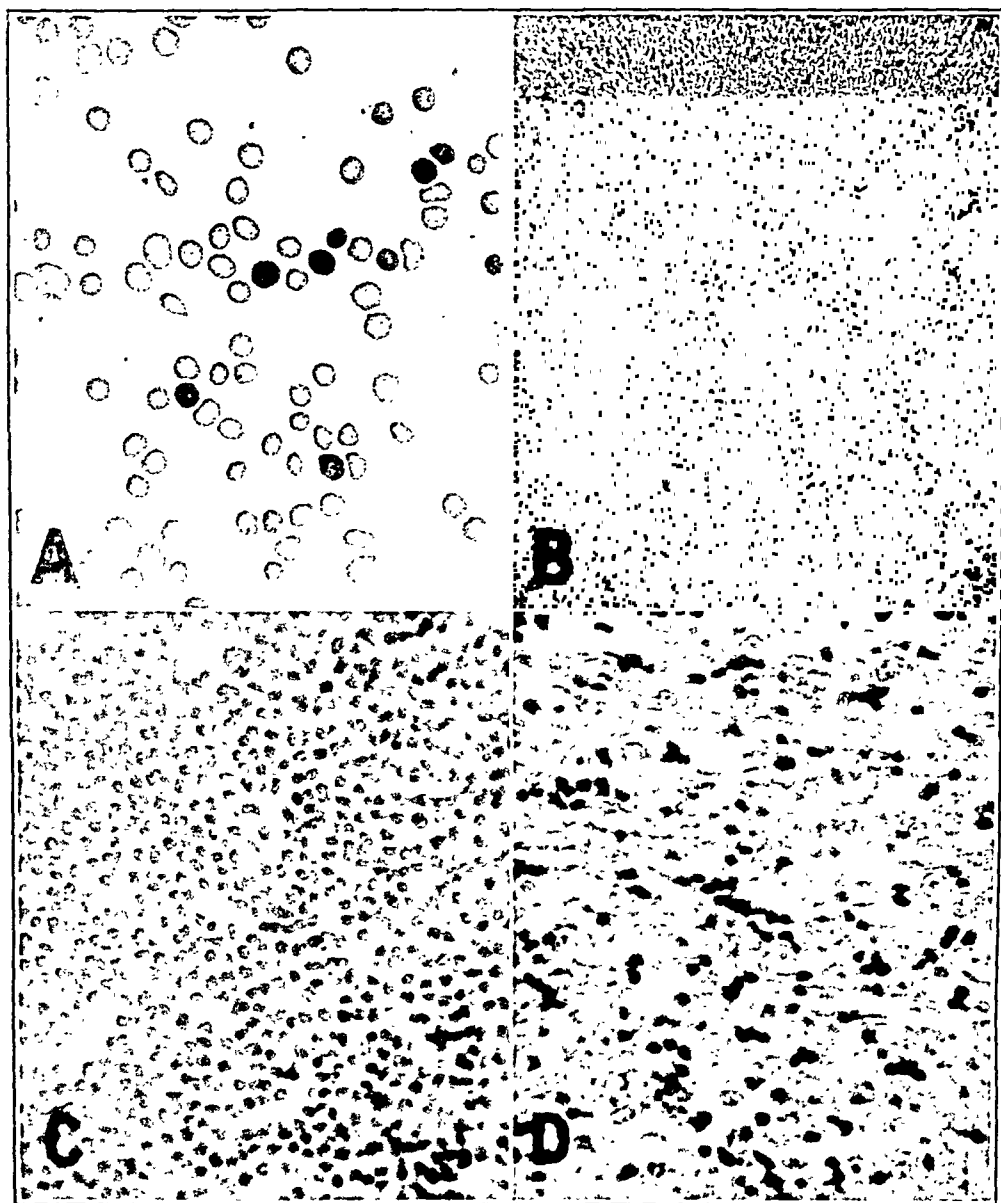


FIGURE 11. White male, 20c. Duration unknown. Radiotherapy, none.

- A. Blood Film: Typical blood picture of chronic lymphatic leukemia with virtually all circulating leukocytes being of well differentiated lymphocytic type (X675).
- B. Biopsy (lymph node): Photomicrograph at low magnification discloses vestiges of follicular lymphoblastoma in one portion of the node (X60).
- C. Biopsy (same lymph node): Other parts of the lymph node have completely lost the follicular pattern and show diffuse sheets of well differentiated lymphocytes, the appearances being consistent with either chronic lymphatic leukemia or a small cell type of lymphosarcoma (X600).
- D. Biopsy (same lymph node): Still other large areas are made up of fairly uniform sheets of anaplastic reticulum cells, conforming to the so-called syncytial type of reticulum cell sarcoma (X600). Note that photomicrographs C and D were taken at the same magnification. (Neg. Nos. PH, NS-1, 2, 3, 4.)

quently encountered change was from Hodgkin's granuloma to Hodgkin's (reticulum cell) sarcoma. Next in order was Hodgkin's paraganuloma to granuloma. Of the 6 paraganulomas that appeared to transform directly to sarcoma, one showed a combination of reticulum cell sarcoma and lymphosarcoma types, the two variants being distinct in separate foci. Two follicular lymphoblastomas underwent transition to Hodgkin's sarcoma, one to granuloma, and one to paraganuloma. Early biopsies on 13 patients disclosed a more poorly differentiated tumor than we found either in later biopsies or at autopsy; it is not clear whether this represented a transition toward better differentiation, or whether the biopsy fortuitously disclosed a local variant of the major type of pattern.

The variety of histologic appearances observed in different foci in the same individual, and even in several areas in the same lymph node, was still more spectacular (Table 3). Thus, 384 of 700 cases presented these combined lesions. In addition to the conventional types of lymphoma, 8 cases showed areas of tumor which, if viewed alone, would justify the diagnosis of fibrosarcoma. This is not particularly odd, however, as fibroblasts are derived from the primitive mesenchyme and participate largely in the granulomatous form of Hodgkin's disease; fibrosarcomatous lesions occurred in patients who had had no radiotherapy, as well as in individuals who were treated. Lymphomas not grouped with Hodgkin's disease also exhibited alteration of their histologic structure in much the same fashion, as indicated in the periphery of the diagram (Fig. 1). This series included many cases of reticulum cell sarcoma which did not obviously develop from Hodgkin's paraganuloma or granuloma, being resulted from a direct transition of follicular lymphoblastoma or lymphosarcoma; such changes are not readily apparent from the scheme of interrelationship presented in Fig. 1, which was devised for the sake of simplification. Tumors at first classified as reticulum cell sarcoma also ended as lymphosarcoma. Likewise, chronic lymphatic leukemia sometimes preceded the development of large tumefactions indistinguishable from lymphosarcoma, and patients with typical lymphosarcoma occasionally produced the blood picture of lymphatic leukemia. An analogous situation occurred with respect to reticulum cell sarcoma and monocytic leukemia. Finally, a few cases of follicular lymphoblastoma terminated as lymphatic leukemia. Our series did not include an instance of monocytic leukemia in which a precursor stage of follicular lymphoblastoma was identified, but this is regarded as a distinct probability.

**Summary.** This study confirms and extends the opinions of other authors that a rigid subclassification of lymphatic tumors is artificial and confusing. Analysis of 1300 lymphatic tumors, many sampled several times during their progress, showed a striking fluidity in histologic pattern, with transitions and combinations that could best be interpreted as indicating a single neoplastic entity having a number of variants.

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All photomicrographs reduced 10% below the magnifications noted in the legends.



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# A HEMATOLOGICAL AND HISTOLOGICAL STUDY OF THE BONE MARROW AND PERIPHERAL BLOOD OF THE ADULT DOG\*

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THE medical literature contains relatively few qualitative and quantitative data on the cellular content of the bone marrow of the dog. More recent publications include the work of Alexandrov,<sup>1</sup> Van Loon and Clark,<sup>11</sup> Stasney and Higgins<sup>10</sup> and Mulligan.<sup>7</sup> Some of these investigators obtained marrow from living dogs by sternal puncture or rib resection. Others obtained marrow for examination from specimens of rib and femur taken at autopsy. The methods employed for these studies included differential counts of the marrow as measured from a smear preparation and sometimes supplemented with an imprint or histopathological examination. The so-called total nucleated cell count was rarely, if ever, employed to indicate the cellularity of the bone marrow.

There have been numerous reports on the normal blood cytology of the dog.<sup>2,4,5,6,8,9</sup>

The purpose of this report is to indicate the findings in the bone marrow of a carefully selected group of normal adult dogs as measured by combined hematological and histological examination.

The hematological picture in the

peripheral blood of normal adult dogs is included.

**Methods.** Adult mongrel dogs of both sexes between 9 to 24 months of age, weighing between 8 and 20 lbs., were used. All dogs were judged normal and in good health by standard laboratory examinations, received a standard kennel ration of Friskies or Purina dog chow, and had been subjected to deworming and distemper vaccination procedures at least one month previously.

The animals were trained to be postured on a table for bleeding purposes. Venepunctures without stasis were made from the jugular vein at a standard time each morning when the animal was in a fasting state. A standard amount of blood was delivered to a small bottle containing a mixture of dried ammonium and potassium oxalate. Samples of blood for the differential white blood cell count and platelet determinations were taken directly from the needle while in the vein.

Red blood cell and total white blood cell counts were made by standard techniques employing haemocytometer diluting Thoma pipettes and Spencer bright line Neubauer counting chambers. All determinations were made in duplicate, and if the results did not check within 10%, recounts were made from the blood in the KNH<sub>4</sub> oxalate bottle.

Differential white blood cell counts

\* This document is based on work performed under Contract Number W-7401-eng-49 for the Atomic Energy Project at the University of Rochester.

were made from cover slip smears stained with Wright's stain. A minimum of 100 cells was counted.

For the platelet counts, the blood was diluted in a red blood cell pipette with platelet solution containing brilliant cresyl blue, sodium citrate and formalin and delivered on to the counting chamber.

Reticulocyte counts were made from cover slip smears containing 1% alcoholic solution of brilliant cresyl blue. One thousand red blood cells were counted and the number of reticulocytes expressed in per cent.

Hemoglobin was determined by diluting a standard volume of the blood sample in a pipette with 0.1 N HCl and comparing the color intensity with that of a standard dichromate solution in a colorimeter (Klett Summerson type) using a green (No. 54) filter. The final value was determined from a standard graph.

Sedimentation rate and hematocrit determinations were made after the method of Wintrobe.<sup>12</sup>

The bone marrow was studied from specimens of rib obtained by rib resection and from ribs, femora, humeri and tibiae obtained at autopsy. The time of sacrifice of the dog was carefully noted and preparations for study were usually executed immediately. In other instances, a marrow specimen remained in the sacrificed dog for a known period of time and was then prepared for examination. In this way it was believed more precise information could be obtained concerning post-mortem changes on the cellular composition of the bone marrow.

The dogs were prepared for rib resection with morphine sulfate supplemented by local infiltration of novocaine. An incision approximately 4 to 6 cm. was made over the rib to be resected and dissection carried down to the periosteum. The periosteum was split lengthwise and dissected from the rib by means of a periosteal elevator. A section of rib near but not involving the costo-chondral junction, approximately 4 to 6 cm. in length, was then resected with the aid of a small circular power saw. The periosteum and wound were closed with multiple interrupted sutures in layers. A section of the

rib so removed was placed in Zenker's fixing fluid for histopathological examination. Hematological examination of the bone marrow was carried out as follows:

**Total Nucleated Cell Count.** A portion of the marrow was squeezed out of the rib, placed in a depression of a drop plate and agitated with a small glass stirring rod to homogenize the specimen. A portion of this marrow was drawn up to the 0.2 mark of a red blood cell pipette and diluted to the 1.01 mark with 2% acetic acid or Turk's solution, giving a dilution of 1 to 500. The pipette and its contents were placed in a shaker and agitated for 15 minutes. The first 3 drops of material were then discarded and the counting chamber filled as for a routine blood count. After allowing the cells to settle in the chamber for 3 minutes, a count was made from the 4 corner squares, each corner comprising 1 cu. mm.

$$\frac{\text{No. Cells counted}}{4} \times 500 (\text{dilution}) \times 10$$

= No. of nucleated cells/mm<sup>3</sup> of marrow. If the count was expected to be either low or high, the dilution factor was varied accordingly.

**Differential Cell Count.** Cover slip smears were made from marrow to which an equal portion of homologous serum had been added. Smears were allowed to dry in the air and were then stained with Wright's stain. A minimum of 500 cells was counted, and the results were expressed in percentages.

An absolute marrow cell count was obtained by multiplying these percentages by the total nucleated cell count.

**Results.** A classification and description of the cells of the bone marrow employed in this study are submitted below. No single cell has been described herein as a common stem cell for both the erythroid and myeloid series. The myeloblast was regarded as the stem cell for the myeloid series and the megaloblast for the erythroid series. No cell was classified into one of these series unless its morphology justified its classification with certainty. Debatable cells were placed in the un-

classified group. Megakaryocytes have been included in this classification. It should be pointed out that the smear technique is not to be considered a satisfactory method for the demonstration of the presence or absence of megakaryocytes.

**MYELOID SERIES.** *Myeloblast:* This was a large cell, 25-30 $\mu$  in diameter, frequently round, with a dark blue, non-granular, usually homogenous and occasionally vacuolated cytoplasm. The nucleus was sharply demarcated from the cytoplasm, filling  $\frac{2}{3}$ - $\frac{3}{4}$  of the cell. It was round, irregular, heavy blue-purple with dark staining properties containing readily discernible nucleoli and fine chromatin material.

*Promyelocyte:* This cell was usually the same size as the myeloblast. The nucleus was slightly smaller, had a more coarse chromatin meshwork and the nucleoli were decreased or absent; the cytoplasm was lighter and sometimes showed early azurophilic granulation.

*Myelocyte:* This cell occasionally showed a decrease in overall size. The cytoplasm was lighter in color with larger granules which were neutrophilic, eosinophilic or basophilic. The nucleus still comprised a large part of the cell, was round or irregular and less sharply demarcated because of the overlying cytoplasmic granulation. The chromatin material was more coarse and nucleoli were absent.

*Juvenile Granulocyte:* This cell was smaller and measured 15-25 $\mu$  in diameter. The most distinctive feature was the indentation of the nucleus which was relatively smaller than the nuclei of the cells previously described. The chromatin structure was finer and the cytoplasm had a paler background in which the granulation was finer and less distinct.

*Stab Neutrophil:* The stab, staff or band cell was recognized by a smaller

S or V or pleomorphic shaped nucleus and chromatin material which was coarse and stained darker than the nuclei of the juvenile granulocytes.

*Segmented Neutrophil:* The last stage in the maturation of the myeloid cell was illustrated by the segmented neutrophil. This cell measured 15-20 $\mu$  in diameter, had a conspicuous segmented nucleus connected by filaments, and the cytoplasm, which was pale and fine, contained indistinct granulations.

The eosinophilic myelocyte series was similar to the neutrophil series except that the cytoplasmic granulation had distinct acidophilic properties. The granules were larger and more refractile. The basophilic series were, likewise, similar to the neutrophil series except that the granulation had basophilic properties.

**ERYTHROID SERIES.** *Megaloblast:* This cell was round, 15-20 $\mu$  in diameter, had a dark blue, homogenous, scanty cytoplasm and a large medium purple, finely granular nucleus in which nucleoli were frequently found. A light or clear zone in the cytoplasm was usually noted.

*Erythroblast:* This cell was smaller than the myeloblast and measured 10-15 $\mu$  in diameter. The cytoplasm was lighter in color and might or might not have had a clear zone. The nucleus was absolutely and relatively smaller with a more coarse dark purple chromatin structure.

*Normoblast:* A further decrease in size was shown, and the cytoplasm presented evidence of containing hemoglobin. The nucleus was less than  $\frac{2}{3}$  the size of the cell and, in some instances, was pyknotic or in the process of extrusion.

*Megakaryocyte:* This cell was readily identified by its large size (30-60 $\mu$ ) and multilobulated nucleus or multinuclei. The cytoplasm was pale

blue and occasionally very finely granular.

*Lymphocyte:* This cell did not differ appreciably from that found in the peripheral blood. Large lymphocytes were rarely found. The cell measured 7-15 $\mu$  in diameter, had a pale, clear blue cytoplasm occasionally containing fine azurophilic granules. The nucleus was relatively large, rounded, usually eccentric and contained dense coarse chromatin. Subdivisions of this group were not deemed advisable.

*Plasma Cell:* This cell measured

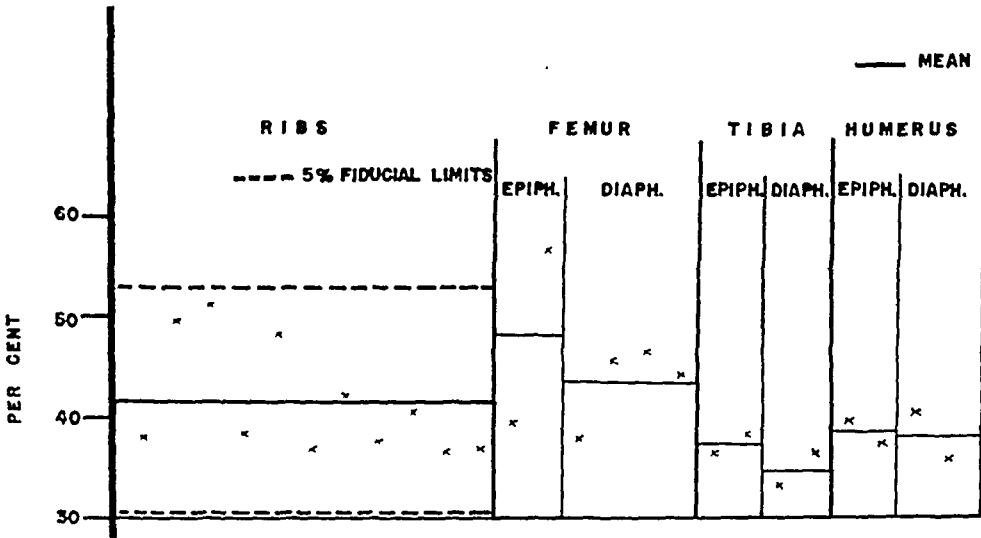


Fig. 1.—Total Erythroid Series from marrow of flat and long bones of a normal dog.

TABLE 1. ANALYSIS OF THE PERIPHERAL BLOOD FOR 91 NORMAL DOGS

Blood Element	Range	Mean	$\sigma$
Red Blood Count (1,000,000/mm <sup>3</sup> )	4.5-8.8	6.22	.697
Hemoglobin (Grams %)	11.2-19.5	14.78	1.730
Reticulocytes (%)	0-2.7	.78	.565
Platelets (100,000/mm <sup>3</sup> )	0-4.2	2.27	.649
White Blood Count (1,000/mm <sup>3</sup> )	545-27,950	10,582	3,544
Absolute Neutrophils (1,000/mm <sup>3</sup> )	3,190-25,994	8,074	3,600
Absolute Lymphocytes (1,000/mm <sup>3</sup> )	0-5,788	1,689	1,019
Differential White Count			
Neutrophils %	42-99	75.11	12.18
Eosinophils %	0-39	6.88	6.48
Basophils %	0-3	.14	.34
Lymphocytes %	0-55	16.82	9.88
Monocytes %	0-4	.15	.54
Mycocytes %	0	0	
Blast Forms %	0-6	.90	1.14
Plasma Cells %	0	0	
Basophilic Stippling	0	0	

CORRECTED SEDIMENTATION RATES FOR 75 NORMAL ADULT DOGS

Sedimentation Rate (mm per hour)			Hematocrit (per cent)		
Range	Mean	$\sigma$	Range	Mean	$\sigma$
0-25	3.3	5.4	40-70	51.3	5.5

TABLE 2. BONE MARROW DIFFERENTIAL COUNT FOR RIBS, FEMORA, TIBIAE AND HUMERI  
Mean Values for Normal Dogs

SERIES	CELL TYPE	RIBS			FEMORA			TIBIAE			HUMERI		
		Mean	$\sigma$		Mean	$\sigma$		Mean	$\sigma$		Mean	$\sigma$	
Myeloid	Myeloblasts	1.77	.92		2.20	.76		2.53	1.26		2.38	1.03	
	Promyelocytes	.44	.56		.23	.50		.21	.39		.48	.80	
	Myelocytes	1.42	.94		1.19	1.24		1.30	1.16		1.74	1.77	
	Juveniles	3.64	2.80		2.36	1.78		3.34	2.86		4.32	2.74	
	Stabs	33.42	7.80		35.01	6.33		34.12	6.14		33.05	3.84	
Total Myeloid*	Neutrophils	2.57	1.72		4.94	2.50		3.70	2.15		4.81	2.50	
	Eosinophils	9.83	5.32		8.39	4.22		9.84	5.14		9.98	5.05	
	Basophils	.41	.84		.20	.22		.41	.58		.53	.67	
	Lymphocytes	53.51	9.71		54.53	7.21		55.45	8.04		57.30	4.05	
	Monocytes	2.16	2.59		1.32	1.49		2.59	2.94		2.62	3.86	
Total Erythroid*	Megaloblasts	0	0		0	0		0	0		0	0	
	Erythroblasts	.28	.34		.14	.30		.12	.19		.08	.15	
	Plasma Cell	32.88	3.76		7.76	.48		7.21	4.32		5.80	3.12	
	Megakaryocyte	40.03	9.94		31.19	5.80		28.13	4.17		28.41	4.99	
	Unclassified	.89	12.02		39.09	9.01		35.46	6.44		34.28	6.72	
Total Unclassified*	Unclassified I	0	0		0	0		0	0		0	0	
	Unclassified II	.91	.58		.85	.82		.66	.47		.92	.03	
	Unclassified III	2.28	2.68		3.17	3.83		4.46	.33		.51	.97	
	No. of Sites	3.41	2.74		4.07	.27		.28	.21		3.34	3.11	
	Ratio	1.34	1.30		3.52	4.92		4.15	4.47		3.96	3.18	
*Total values are means of sums of all dogs rather than sums of means. Therefore, agreement of sum of means with the total mean is only approximate.		35	8		16	16		8	8		8	8	

10-15 $\mu$  in diameter, had a round, perinuclear clear area and a fairly dark blue, homogenous cytoplasm with a light zone in it. The nucleus was relatively small, eccentric and rounded in

which the chromatin material was coarse and sometimes had a cartwheel pattern.

*Unclassified Cells:* When cells were found to present a fairly consistent

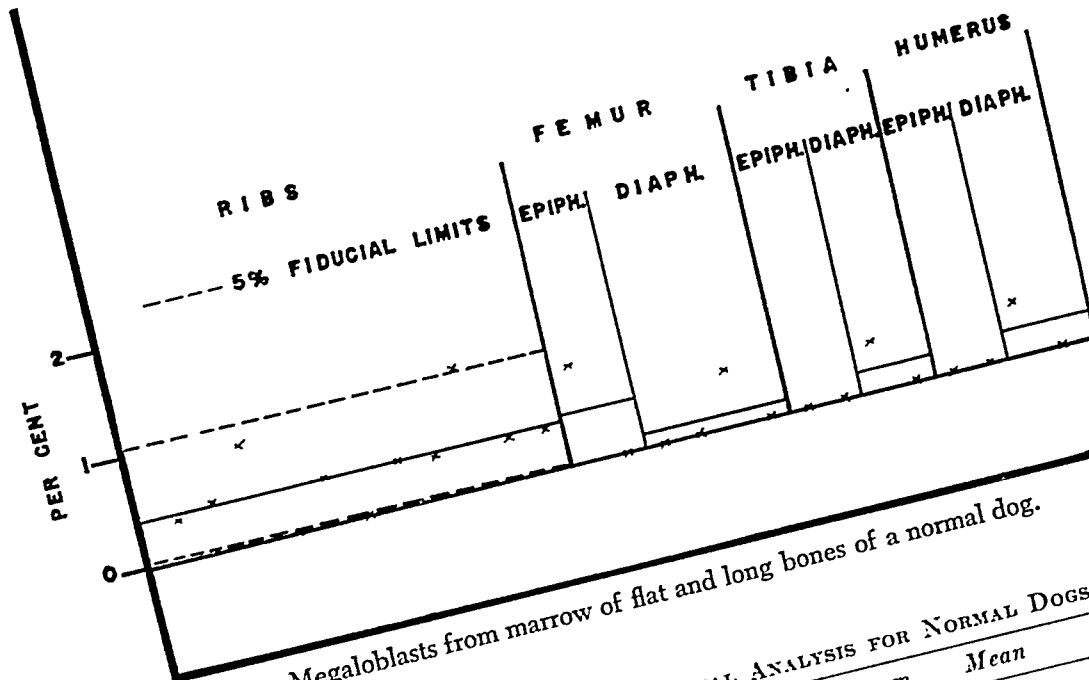


Fig. 2.—Megaloblasts from marrow of flat and long bones of a normal dog.

TABLE 3. RIB BONE MARROW DIFFERENTIAL ANALYSIS FOR NORMAL DOGS					
Series	Cell Type	Minimum	Maximum	Mean	Sigma
Myeloid	Myeloblasts	.23	3.66	1.89	.90
	Promyelocytes	0	3.26	.65	.97
	Myelocytes	0	9.47	2.73	2.40
	Juveniles	0	24.44	5.12	4.12
	Stabs	16.46	62.88	42.37	9.14
	Neutrophils	.24	14.29	5.01	3.41
	Eosinophils	.23	19.30	4.72	3.98
	Basophils	0	1.25	.19	.80
	Lymphocytes	0	90.07	62.68	11.78
	Monocytes	36.71	8.05	.73	1.42
Total Myeloid*	Megaloblasts	0	0	0	.38
	Normoblasts	0	1.33	.27	3.09
	Erythroblasts	0	11.22	4.64	10.24
	Plasma Cell	0	53.92	28.24	11.60
	Megakaryocyte	0	60.50	33.15	.66
	Unclassified I	7.98	2.08	.39	.21
	Unclassified II	8.72	1.10	.06	.60
Total Erythroid*	Plasma Cell	0	2.47	.78	2.88
	Megakaryocyte	0	15.51	1.97	.34
	Unclassified I	0	1.46	.26	3.00
	Unclassified II	0	15.74	1.89	
	Unclassified III	0			
Total Unclassified*					
Myeloid/Erythroid Ratio					

Analysis Computed from 36 Dogs.

\* Total values are means of sums of all dogs rather than sums of means. Therefore, agreement of sum of means with the total mean is only approximate.

picture but still could not be classified in the above groups, they were placed in subgroups as follows:

1. Cells of the erythroid and myeloid series that were undergoing mitotic and amitotic division.

2. Cells similar to small lymphocytes. These cells contained such a small amount of cytoplasm that identification was difficult.

3. These cells varied in size from  $5-20\mu$  in diameter, had a grayish blue cytoplasm which sometimes contained large blue granules and was occasion-

ally vacuolated. The nucleus was rarely distinguishable; if present, it occupied  $\frac{1}{4}$  of the cell.

36 dogs. A survey of these tables shows that there is a definite similarity in the percentage distribution of the bone marrow cells in the 4 areas studied and between the diaphysis and epiphysis of the long bones. The myeloid-erythroid ratio is similar in all areas.

The means of the total nucleated cell count for femora, tibiae and humeri for the same 4 dogs individually are given in Table 4. The cellularity of the bone marrow from various regions of the body is compared. These data

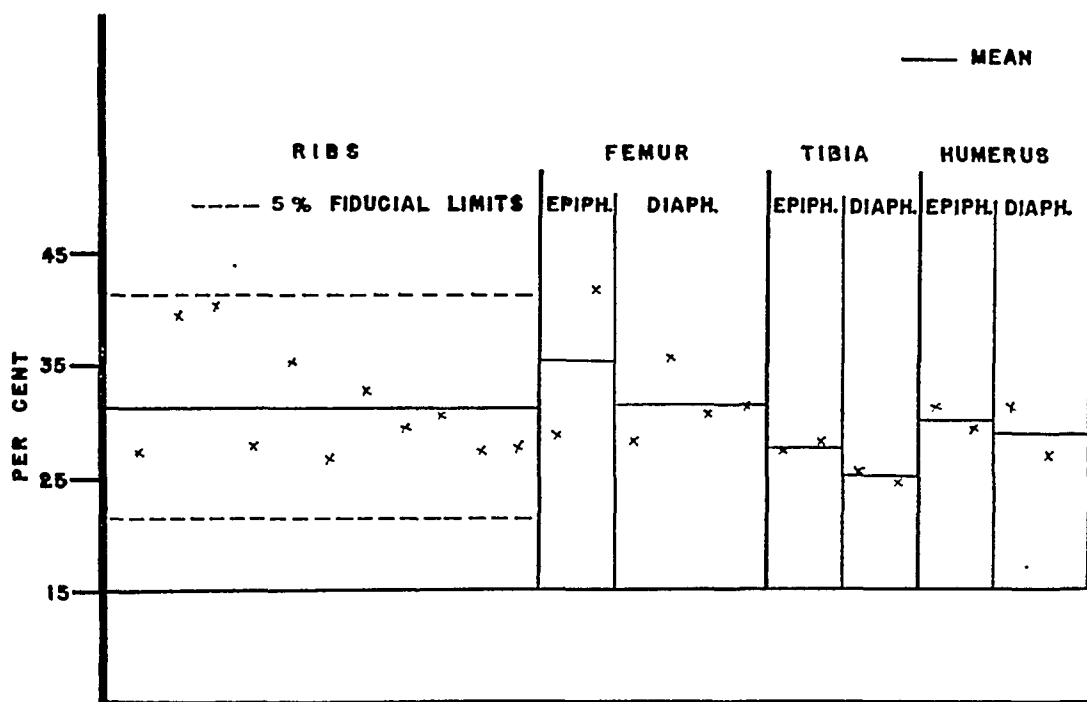


Fig. 3.—Erythroblasts from marrow of flat and long bones of a normal dog.

ally vacuolated. The nucleus was rarely distinguishable; if present, it occupied  $\frac{1}{4}$  of the cell.

An analysis of the peripheral blood for 91 normal, adult dogs is presented in Table 1. These data are in general agreement with those of Van Loon and Clark<sup>11</sup> and others.

Data from the marrow differential counts of the ribs, humeri, femora and tibiae for a group of 4 dogs are shown in Table 2 and Figures 1 to 7 while Table 3 presents rib marrow data from

indicate that rib marrow is uniformly cellular throughout, whereas the cellular density of the long bones undergoes wide variations.

Table 5 compares the cellularity and differential counts in several rib sites of the same dog. These data indicate that bone marrow from various ribs presents a uniform picture with respect to cellular density and distribution.

The effect of time after death on rib marrow is shown in Table 6. No significant differences in the percent-



TABLE 4. BOSE MARROW TOTAL NUCLEATED CELL COUNTS

DOG	RIBS	FEMUR			TIBIA			HUMERUS	
		Epiphysis (2)*	Diaphysis (1)	Mean Values	Epiphysis (2)	Diaphysis (2)	Epiphysis (2)	Diaphysis (2)	Diaphysis (2)
1	(9)*	721,250	21,875	555,000	625		339,375		190,000
	1,794,792								361,875
2	(10)	934,375	119,062	325,000	25,625		1,028,125		1,992,500
	787,750								
3	(11)	2,255,625	1,884,375	1,306,250	1,235,000		2,204,375		840,625
	1,118,091								
4	(8)	576,250	509,062	1,200,625	13,125		662,500		
	948,750								

\* Figure on parenthesis indicates number of specimens studied.

TABLE 5. BOSE MARROW ANALYSIS OF VARIOUS RIB SITES FROM THE SAME DOG

TABLE 6.									
		8 RIB RT.		8 RIB LT.					
SERIES	CELL TYPE	2.59	.51	2.53		5.25	0	5.25	1.186
Myeloid	Megakaryoblasts	0	0	0		6.38	0	6.38	4.652
	Promyelocytes	5.39	.76	8.05		3.55	5.69	37.12	.690
	Myelocytes	3.45	4.55	3.45		8.27	6.19	7.58	.735
	Juveniles	38.79	17.98	37.01		5.20	42.57	4.10	1.107
	Stabs	7.33	7.92	8.28		.24	3.96	.05	1.732
	Neutrophils	3.67	3.28	4.37		62.88	0	63.60	.130
Total Myeloid*	Eosinophils	0	0	0		.24	65.84	.14	0
	Basophils	61.21	64.39	63.68		0	0	.23	1.184
	Lymphocytes	.22	0	0		.24	0	27.53	3.117
	Monocytes	0	0	0		28.13	27.97	4.15	2.076
	Megakaryoblasts	25.43	28.28	27.82		2.13	2.48	31.90	.192
	Erythroblasts	9.48	2.27	4.37		30.50	30.45	.09	.103
Total Erythroid*	Normoblasts	35.13	30.56	32.87		0	0	.05	.125
	Plasma Cell	0	0	0		0	0	.85	1.435
	Megakaryocyte	.43	1.01	.69		.71	0	3.38	0
	Unclassified I	.86	3.79	2.92		5.67	2.97	0	1.388
	Unclassified II	2.16	0	2.30		6.38	0	4.23	
	Unclassified III	0	1.80	3.22		2.06	3.71	1.99	75.263.1
		3.02	2.11	1.94		960,000	1,076,250	1,081,750	
				1,118,750					
*Green is only approximate.									

Therefore, agreement of sum of means with the total mean is only approximate.

\* Total values are means of sums of all dogs rather than sums of means.

TABLE 6. RIB BONE MARROW ANALYSIS FOR NORMAL DOGS  
Mean Values

SERIES	CELL TYPE	HOURS AFTER DEATH					
		0	2	3	4	5	8
Myeloid	Myeloblasts	1.56	.93	.56	3.25	.30	0
	Promyelocytes	.44	.55	0	1.18	0	0
	Myelocytes	1.18	.61	0	1.18	.30	0
	Juveniles	3.25	1.47	.28	2.78	0	0
	Stabs	31.54	31.06	28.81	42.78	17.76	30.04
	Neutrophils	2.53	1.79	.96	.24	1.88	1.74
	Eosinophils	8.73	8.70	8.60	9.76	1.70	5.20
	Basophils	.59	.10	0	0	.30	0
	Lymphocytes	49.82	45.20	39.22	61.16	22.26	36.98
	Monocytes	1.03	.29	5.44	0	0	6.08
Total Myeloid*	Megakaryocytes	0	0	0	0	0	0
	Megakaryoblasts	.26	.17	0	0	.48	0
	Erythroblasts	37.49	36.42	36.96	25.18	46.65	36.46
	Normoblasts	8.02	13.64	16.98	11.36	18.31	18.23
	Plasma Cell	45.77	50.23	53.94	36.54	65.45	54.69
Total Erythroid*	Megakaryocyte	.92	1.00	1.40	.92	.30	2.26
	Unclassified I	0	0	0	0	0	0
	Unclassified II	.94	.18	0	.23	0	0
	Unclassified III	1.33	3.10	0	.92	11.98	0
	Unclassified IV	.20	0	0	.23	0	0
Total Unclassified*	Unclassified V	2.47	3.28	0	1.38	11.98	0
	No. of Sites for Differential Count	14	6	2	2	2	2
	Total Nucleated Cell Count	1,371,771	1,460,625	1,722,500	957,500	1,775,000	1,998,750
Myeloid/Erythroid Ratio	No. of Sites for Nucleated Count	14	6	2	4	2	2
	Myeloid/Erythroid Ratio	1.09	0.90	0.73	1.67	0.34	0.68

\* Total values are means of sums of all dogs rather than sums of means. Therefore, agreement of sum of means with the total mean is only approximate.

ages or total nucleated cell counts are shown for the period studied.

Histological records of the rib and diaphysis of the femur are shown in Figures 8, 9.

**Discussion.** These results indicate that the cellular distribution as found in a given sample of bone marrow from one area of the body will be representative of the marrow picture from the rest of the body. This finding is in agreement with the observation of Stasney and Higgins.<sup>10</sup>

Bone marrow may be divided into 2 types: the more and constant cellular as found in the flat bones, and the less and more varied cellular as found in the long bones. However, there may be centers of hematopoietic activity distributed throughout the fatty marrow in the long bones. This is especially so adjacent to the endosteum and near the epiphysis. Thus the degree of cellularity of the flat bones in a normal or pathological state may be appraised by a total nucleated cell count or a histological preparation, but these determinations carry less signifi-

cance in evaluating the fatty types of marrow. The sampling of marrow from the flat bones, such as the rib or sternum, will give not only an index of the cellular pattern but an index of the degree of cellularity as well. When sampling marrow bearing areas by needle and aspiration technique, local hemorrhage is invariably produced resulting in dilution of the marrow material by the shed blood. Subsequent samplings from the same site are altered by the reparative process from the previous hemorrhage. This reparative process is a slow one extending over many weeks, and residual damage can usually be detected months later, especially in the long bones.

Histological examination of the bone marrow entails many limitations, chief of which is lack of detailed individual cellular morphology and the associated inaccurate cellular identification. However, the megakaryocytes as well as the anatomical relationship of the marrow cells to other tissues in the marrow bearing region can be studied better.

A significant alteration in cellularity

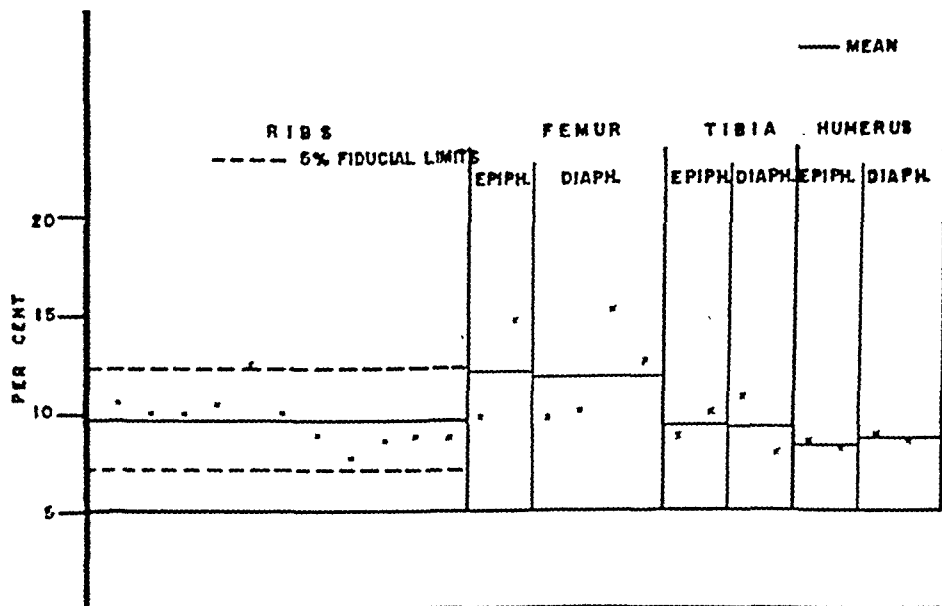


FIG. 4.—Normoblasts from marrow of flat and long bones of a normal dog.

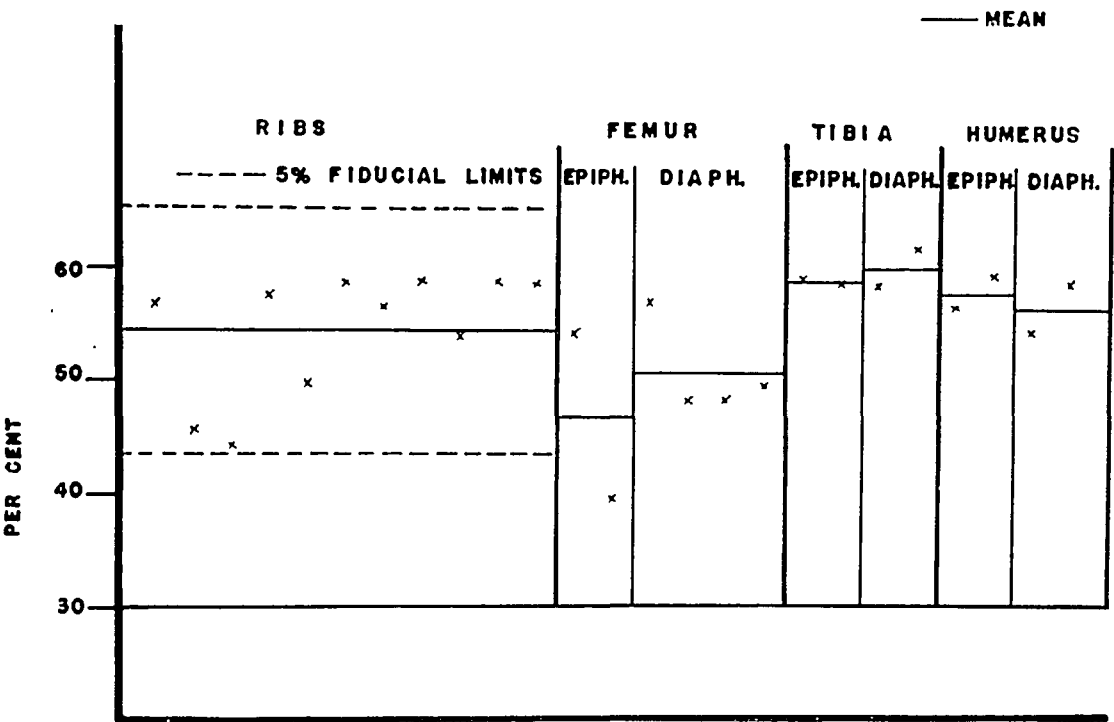


Fig. 5.—Total Myeloid Series from marrow of flat and long bones of a normal dog.

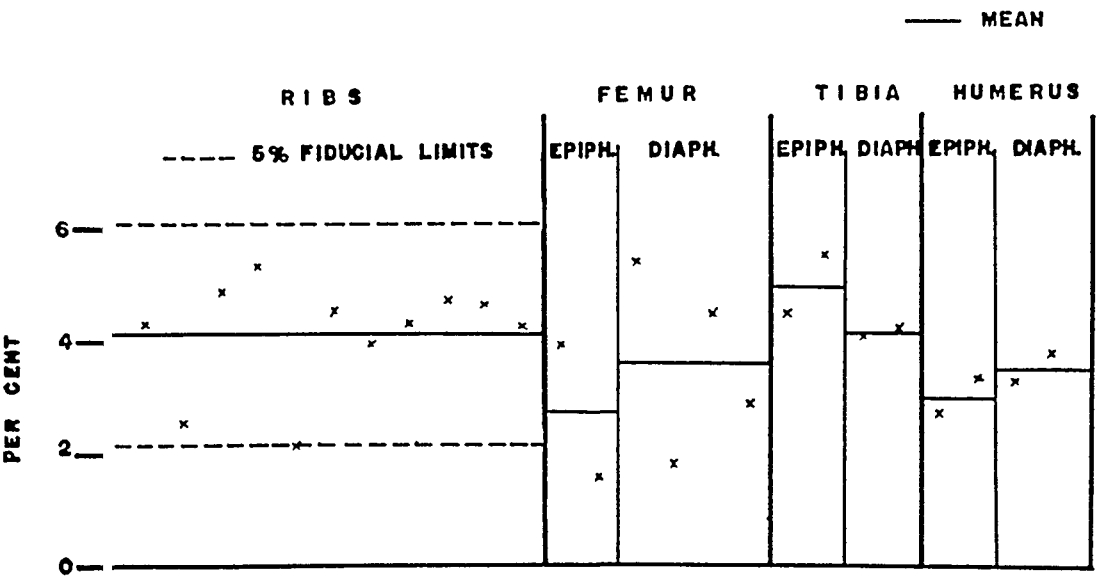


Fig. 6.—Myeloblasts, Promyelocytes and Myelocytes from marrow of flat and long bones of a normal dog.



low values in the ranges of the peripheral blood was the result of, in most instances, isolated findings. The animals selected for this study were judged normal by conventional clinical standards but by hematological standards might not be accepted as normal.

**Summary.** 1. The bone marrow of ribs, femora, tibiae and humeri and the peripheral blood of adult normal dogs have been studied and the findings tabulated.

2. Methods for examination of the bone marrow of the dog are described.

3. Cellular distribution was shown to be fairly uniform throughout the marrow bearing areas of the dog, whereas the cellularity exhibited wide variations.

4. A significant alteration in degree of cellularity and cellular detail was not found in the bone marrow within the first 8 hours after death.

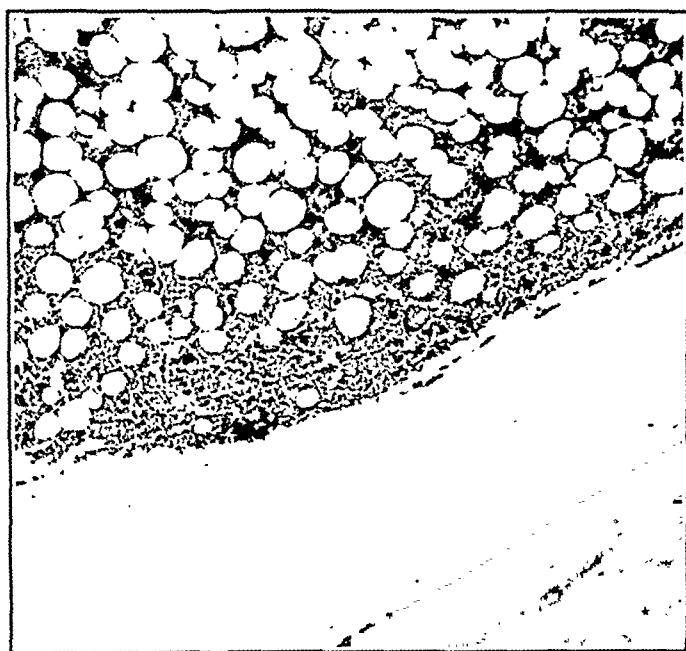


Fig. 9.—Marrow from diaphysis of femur of normal dog. Nucleated cells count 119,000 cells/mm<sup>3</sup> ×100.

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# THE NEGATIVE EFFECT OF FOLIC ACID ON IRRADIATION LEUKOPENIA IN THE CAT\*

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THE hemopoietic tissues are extremely sensitive to a variety of toxic agents such as: thiouracil, the sulfonamides, certain heavy metals, dinitrophenol, amidopyrine and roentgen irradiation. This sensitivity is reflected by alterations within these tissues and many times in the corpuscular elements of the peripheral blood resulting in anemia, leukopenia and thrombocytopenia. The attempts of physicians to prevent or correct these disorders by the administration of a variety of drugs have met with dismal failure. Certainly it must be admitted that the results of administration of pentnucleotide (to mention one drug) in granulocytopenia have been far from spectacular.

Following the isolation and synthesis of folic acid in 1945 and 1946 by Angier *et al.*,<sup>1</sup> this substance has been used widely in a variety of hemopoietic disorders. Watson *et al.*<sup>4</sup> have suggested that this drug may be useful in the correction of irradiation leukopenia. They obtained beneficial effects in humans receiving regional roentgen treatment for various types of malignancy. Therefore it was thought important to investigate the possible prophylactic and therapeutic value of folic acid in cats receiving whole body irradiation. It is realized that the situation which exists in human beings receiving regional irradiation is not strictly com-

parable to the whole body irradiation to which our cats have been subjected. Also the figures as given by Watson *et al.*<sup>4</sup> pertain to humans receiving repeated small doses of radiation in cases of malignancy, whereas this report deals with apparently normal cats receiving 200r at a single exposure.

**Method:** Twenty-six cats have been studied. They have been divided into 3 groups: Group I (6 cats) received both oral (50 mg.) and subcutaneous (30 mg.) folic acid\*\* daily for one week prior to the exposure to 200r whole body irradiation.† The folic acid was continued for 3 weeks following exposure to roentgen radiation. Daily white blood cell counts and differential studies were done for one week prior to irradiation and for one month subsequent to irradiation. All white blood cell counts were done with Bureau of Standards equipment.

**Group II (9 cats).** These animals received 50 mg. of folic acid subcutaneously daily for one week prior to Roentgen ray exposure. Folic acid was continued one month following such exposure. Subsequent study was the same as for Group I.

**Group III (11 cats).** These animals were kept as controls—that is they were exposed to the effects of 200r whole body irradiation and were not given folic acid. Follow-up study was the same as for animals in Group I.

**Results.‡** These are shown clearly in Figs. 1, 2, 3, 4, and 5 which are a comparison of the normal and the control means of the various white blood cell elements. No difference between the control and the experimental animals can be detected.

It can also be seen in Tables 1, 2 and 3 that there is no difference in the response to roentgen irradiation of cats given folic acid and those that were given no folic acid.

There also was apparently no difference between the cats in Group I and

Group II. In other words, the route of administration of folic acid apparently did not influence the results.

Discussion. According to the theory of Stokes<sup>3</sup> folic acid acts as an enzyme or co-enzyme in the formation of thymine which is in turn converted

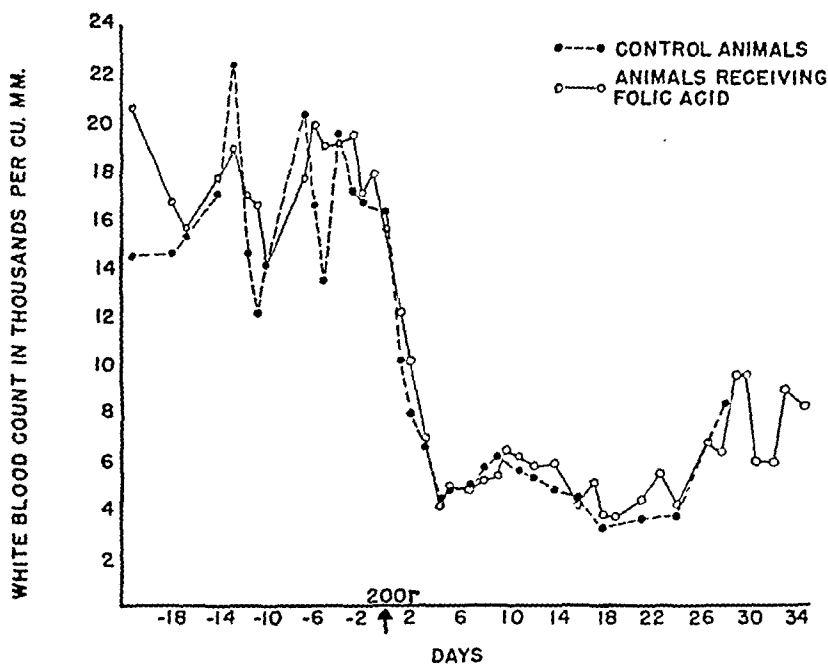


FIG. 1. A comparison of the effect of 200r roentgen irradiation on the level of the white blood count in cats receiving folic acid and in cats held as controls (receiving no folic acid).

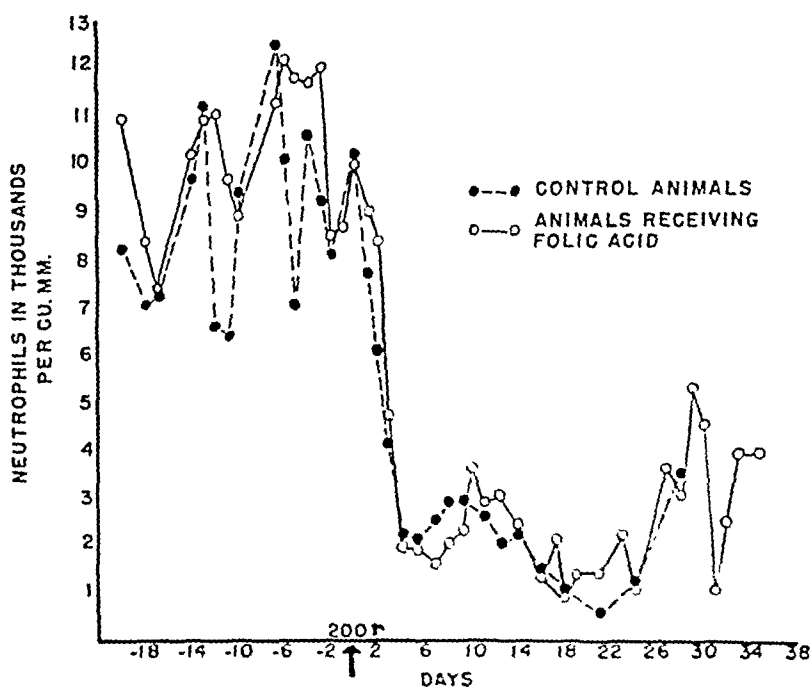


FIG. 2. A comparison of the effects of 200r roentgen irradiation on the level of the neutrophils in cats receiving folic acid and in cats held as controls (receiving no folic acid).



to nucleic acid, an integral part of the structure of the cell nucleus. There are many other theories as to the mode of action of folic acid but the discovery of its exact rôle in hemopoiesis must await further investigation. However, it may be said that folic acid probably plays an important rôle in normal hemopoiesis and that the lack of this substance may result in granulocytopenia and, or, anemia. Recently the effects of folic acid in the correction of various types of leukopenias have been stud-

ied by Kornberg *et al.*<sup>2</sup> The purpose of our investigation was to discover if possible if there were any beneficial effects obtained by the prophylactic or therapeutic administration of folic acid to cats receiving whole body roentgen irradiation. (It had been hoped, if such a beneficial effect could be obtained with folic acid, that it would be apparent by using an amount of roentgen radiation which was below the LD 50 for cats but yet sufficient to produce leukopenia in all instances.) This calcu-

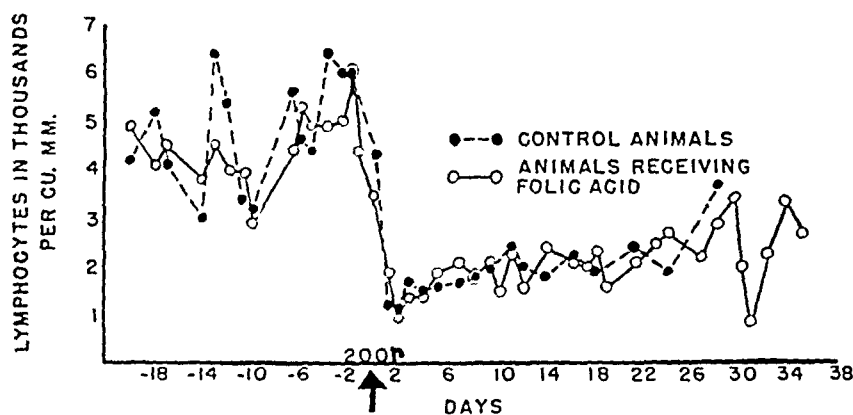


FIG. 3. A comparison of the effect of 200r roentgen irradiation on the level of the lymphocytes in cats receiving folic acid and in cats held as controls (receiving no folic acid).

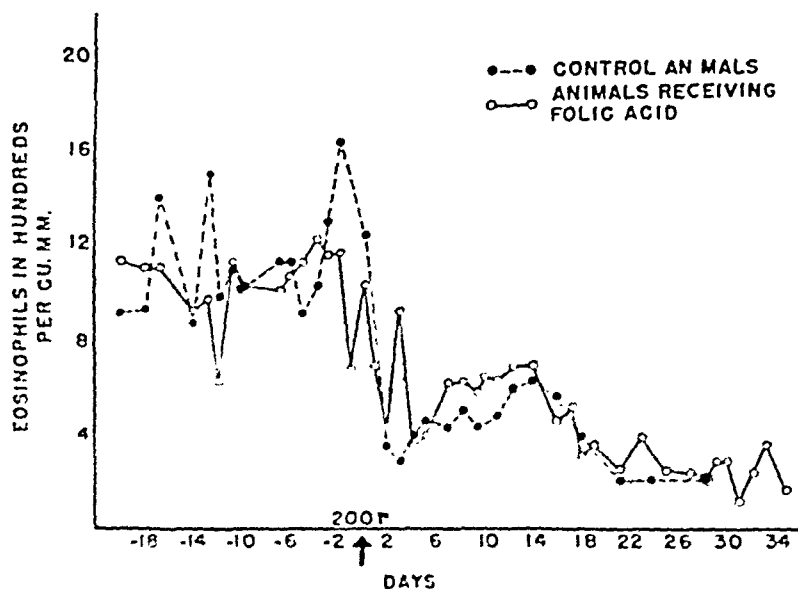


FIG. 4. A comparison of the effect of 200r roentgen irradiation on the level of the eosinophils in cats receiving folic acid and in cats held as controls (receiving no folic acid).

lated dose was 200r whole body radiation. As noted under Results, as well as in Tables 1, 2, and 3 and Figures 1, 2, 3, 4, and 5 no difference was found between the control and the experimental animals. The production of leukopenia by roentgen radiation was almost identical in the control and folic acid groups. Also the differential formulas were approximately the same in

the two groups. No difference was detected in the response of animals in Group I and Group II—that is, the route of administration of folic acid did not alter the response to roentgen radiation.

It is difficult to understand how folic acid could protect against the effects of roentgen radiation. Exactly how radiant energy damages the function of

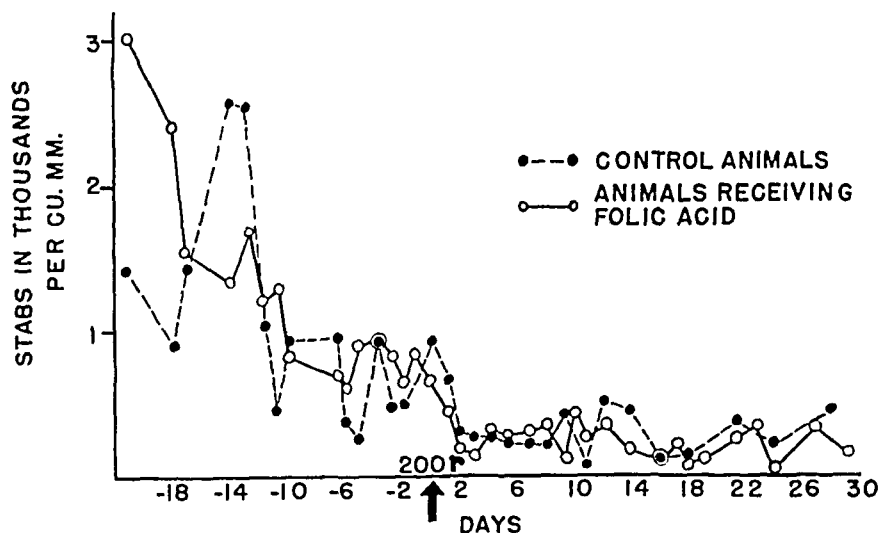


FIG. 5.—A comparison of the effect of 200r roentgen irradiation on the levels of the stabs (band forms) in cats receiving folic acid and in cats held as controls (receiving no folic acid).

TABLE 1.—CATS GIVEN ORAL AND SUBCUTANEOUS FOLIC ACID PRIOR TO AND FOLLOWING 200R WHOLE BODY ROENTGEN IRRADIATION

Cat Number	Average pre-irradiation WBC per cu. mm.	Average post-irradiation WBC per cu. mm. for week during maximum leukopenia	Maximum drop %	Average post-irradiation WBC per cu. mm. during entire period	Average drop %
1	12,160	3,933	67.7	4,003	67.1
2	29,103	5,825	80.0	8,140	72.0
3	14,672	5,150	64.9	5,522	62.4
4	23,606	6,058	74.3	6,334	73.2
5	15,825	5,783	63.5	7,072	55.3
6	14,353	4,350	69.7	4,650	67.6
Average	18,287	5,200	71.6	5,950	67.5

TABLE 2.—CATS GIVEN SUBCUTANEOUS FOLIC ACID PRIOR TO AND FOLLOWING 200R WHOLE BODY ROENTGEN IRRADIATION

Cat Number	Average pre-irradiation WBC per cu. mm.	Average post-irradiation WBC per cu. mm. for week during maximum leukopenia	Maximum drop %	Average post-irradiation WBC per cu. mm. during entire period	Average drop %
7	11,175	2,820	74.8	3,785	66.1
8	18,175	6,180	66.0	8,400	53.8
9	11,775	3,400	71.1	4,508	61.7
10	20,000	4,840	75.8	5,100	74.5
11	30,100	9,540	68.3	9,238	69.3
12	11,225	3,000	73.3	3,186	71.6
13	19,850	4,540	87.1	6,371	67.9
14	23,200	8,900	61.6	8,769	62.2
15	12,925	5,120	60.4	4,692	63.7
Average	17,603	5,371	69.5	6,005	65.9

hemopoiesis is not known, but whatever the mechanism, it is clear that folic acid does not protect against such damage. However, it should not be construed that these results are comparable to figures in which partial or regional roentgen treatment is employed. It is not inconceivable that some of the leukopenias which develop during the course of prolonged roentgen treatment, particularly of the tho-

rax and abdomen, result from interference in the production, absorption, or utilization of substances such as folic acid by virtue of the effects of Roentgen-rays on the gastro-intestinal tract.

**Summary.** The prophylactic and therapeutic administration of folic acid to cats did not alter the occurrence or the magnitude of leukopenia caused by exposure to 200r whole body irradiation.

TABLE 3.—CATS GIVEN ONLY 200r WHOLE BODY ROENTGEN IRRADIATION AND NO FOLIC ACID

Cat Number	Average pre-irradiation WBC per cu. mm.	Average post-irradiation WBC per cu. mm. for week during maximum leukopenia	Maximum drop %	Average post-irradiation WBC per cu. mm. during entire period	Average drop %
16	11,044	8,066	81.3	6,656	39.7
17	17,628	5,508	68.8	3,172	53.6
18	15,393	3,783	75.4	4,063	73.6
19	10,793	2,267	79.0	3,142	70.9
20	22,556	5,842	74.1	5,797	74.3
21	19,054	5,542	71.0	7,688	59.7
22	19,200	5,120	73.3	6,923	63.9
23	18,475	3,880	79.0	4,292	76.8
24	33,650	5,140	84.7	5,320	84.2
25	19,925	8,180	59.0	6,938	65.2
26	15,050	3,575	76.3	5,467	63.7
Average	18,436	5,173	74.7	5,860	68.4

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# SEVERITY AND DURATION OF HYPERTENSION IN RELATION TO AMOUNT OF CARDIAC HYPERTROPHY\*

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HYPERTENSION, an accepted cause of cardiac hypertrophy, was mentioned by Bright<sup>3</sup> in 1836. Investigators of the relationship between duration and severity of hypertension on the one hand, and amount of cardiac hypertrophy on the other hand, however, have reached various conclusions.<sup>6,7,18</sup> In addition, studies more or less relevant to ours have had to do with the following: (1) the different effects on cardiac hypertrophy of malignant or mild hypertension<sup>13</sup>; (2) the onset of hypertension and the associated early fluctuant blood pressure<sup>9,14</sup>; (3) the effect of sex on the prognosis of hypertension<sup>2</sup>; (4) cardiac hypertrophy of rheumatic heart disease<sup>10,19</sup>; (5) the effect on cardiac hypertrophy of congestive failure or its absence in cases of coronary arteriosclerosis,<sup>5</sup> and, (6) the role of coronary sclerosis in the development of cardiac hypertrophy.<sup>1,4,8,11,12,16</sup> Our purpose here is primarily to add the results of our study to reports already printed.

**Materials and method.** Among the records of necropsies performed at the Mayo Clinic in the 6 years beginning with January 1, 1940, are 111 which represent cases in which normal readings of blood pressure had been obtained on one or more occasions but in which, nevertheless, hypertension subsequently had developed. As far as possible, records of cases in which valvular heart disease had existed were excluded.

Although the blood pressure and the severity of hypertension are not always closely related to the funduscopic changes, yet when record of the last mentioned findings was

available, the severity of the hypertension was grouped<sup>17</sup> on the basis of them. When record of examinations of the ocular fundus was not available, the hypertension was grouped (except with reference to Group 4) according to arbitrary ranges of blood pressure. The lower limit of Group 2 was taken to be 200 millimeters of mercury systolic and 100 diastolic, and that for Group 3 was established as 240 systolic and 120 diastolic. Group 4 was recognized only if funduscopic examination had been performed.

To determine, from the records, how long hypertension had endured in each of the 111 cases was not entirely simple. Hypertension had ended, presumably, when the patient died, a date easily determined. When, however, had the hypertension begun? Patients had not been examined daily, of course. They had come to the clinic, had gone away and had returned. A long time might elapse between two successive examinations and it might be at some time in this interval that the hypertension had begun. Whether the condition had begun near the start or near the end of the interval could not be known. Therefore, the condition would have to be considered to have had its inception when the patient was examined for the last time before an interval of absence or when he was examined for the first time after an interval of absence. The former of these dates would be the start of a maximal period of hypertension; the latter, the start of a minimal period of hypertension. The maximal duration of hypertension in a given case, therefore, was considered to date from the last time that the patient had been seen at the clinic with the systolic or the diastolic blood pressure, or both, persistently less than 140/90. The minimal duration of hypertension, on the other hand, was considered to date from the first time that the systolic or the diastolic blood pressure, or both, were known to have risen to 140/90 or above. If hypertension of a

\* Abridgement of thesis submitted by Dr. Stein to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

lower group was succeeded by hypertension of a higher group, the duration of the disease was considered to be the sum of the duration of the hypertension of both groups. The average of maximal and of minimal duration has not been determined, for the quantities vary so widely that an average would not be reliable or significant.

In each instance, the heart had been weighed after the pericardium had been removed, the great vessels had been severed at their origins and the heart and great vessels had been opened and washed clean. What the normal weight of the heart would have been was calculated by multiplying the body weight of the patient by the appropriate factor as determined by H. L. Smith<sup>15</sup>. To exclude the possibility of a low estimate, and a consequently erroneous acceptance of the presence of hypertrophy, 20% was added to the calculated normal weight of the heart and the result was taken to be the calculated maximal normal weight of the heart. The hypertrophy was calculated as a percentage above this calculated maximal normal weight.

**Observations.** In the 111 cases reviewed (in which 65 of the patients were men and 46 were women) hypertrophy, in terms of the weight of the heart, varied from 0 to 176% more than

the calculated normal. The average for the series was 46.8%.

The percentage of cardiac hypertrophy, when compared with the severity (group), and with the duration, of hypertension, gave some expected, and some unexpected, results. The percentage of hypertrophy appeared to be closely related to the severity (group) of the hypertension. Thus, in Table 1 it is demonstrated that the average percentage of hypertrophy was approximately twice as much in cases of hypertension of Group 4 as in cases of Group 1. On the other hand, no relationship appeared to exist between the percentage of cardiac hypertrophy and the duration of hypertension. These data are included in Tables 2 and 3. Except in hypertension of Group 4, moreover, no relationship could be observed between the severity (group) of the hypertension and its over-all duration; this is not shown in any of the tables published herewith. Five of the

TABLE 1.—THE PERCENTAGE OF CARDIAC HYPERTROPHY AND THE SEVERITY (GROUP) OF HYPERTENSION

Hypertrophy %	Groups of hypertension				Total, cases
	Group 1, cases	Group 2, cases	Group 3, cases	Group 4, cases	
0-19	20	8	2	0	30
20-39	16	7	1	0	24
40-59	12	3	2	3	20
60-79	13	5	4	0	22
80-99	4	0	1	2	7
100-119	2	1	2	1	6
120-139	1	1	0	0	2
140+	1	0	0	1	2
Total, cases	69	23	12	7	111
Average hypertrophy, %	43.5	36.9	60.1	87.6	46.8

TABLE 2.—THE MINIMAL DURATION OF HYPERTENSION AND THE PERCENTAGE OF CARDIAC HYPERTROPHY

Hypertrophy, %	Minimal duration, years				Total, cases
	0-4	5-9	10-14	15-19	
0-19	13	4	5	3	30
20-39	8	4	3	1	24
40-59	8	5	2	5	20
60-79	7	2	4	6	20
80-99	2	4	0	0	7
100-119	3	0	1	0	6
120-139	1	1	0	0	2
140+	2	0	0	0	2
Total, cases	42	20	15	15	111
Average hypertrophy, %	48.9	51.4	38.1	47.6	46.8

7 patients whose hypertension had been of Group 4 had had severe glomerulonephritis, with a rapidly terminal course and consequent brief duration of the hypertension.

Once again, cardiac hypertrophy, when considered together with duration of hypertension, led to some impressions concerning the relative tolerance of persons of the two sexes to hypertension. In 6 of the 10 cases in which hypertrophy was greater than 100%, the patients were known to have had hypertension for less than 5 years. Of these 10 patients, 7 had been men. At necropsy, the weights of the hearts of only 4 patients in the series failed to exceed the normal, as determined by the criteria previously defined. In each of these 4 instances the patient was a woman. The minimal duration of hypertension in these 4 cases varied from 12 to 15 years. Moreover, in Table 4, it is evident that the percentage of males dwindled as the minimal du-

ration of hypertension increased; the percentage of females, on the other hand, remained fairly constant. If it is considered that it was the hypertension which had caused death in these 111 cases, it seems that the women had withstood their hypertension better than the men.

**Summary.** In a series of 111 cases in which blood pressure once had been observed as normal but hypertension subsequently had developed, records of necropsy were reviewed. The percentage of cardiac hypertrophy appeared to be directly related to severity (group) of hypertension but unrelated to duration of hypertension. Moreover, except in hypertension of Group 4, relationship could not be found between severity (group) of hypertension and duration of hypertension. The women of the series seemed to have withstood their hypertension better than the men.

TABLE 3.—THE MAXIMAL DURATION OF HYPERTENSION AND THE PERCENTAGE OF CARDIAC HYPERTROPHY

Hypertrophy, %	Maximal duration, years						Unknown	Total, cases
	0-4	5-9	10-14	15-19	20-24	25+		
0-19	3	5	3	6	0	2	11	30
20-39	2	4	2	1	3	2	10	24
40-59	4	2	3	3	2	1	4	19
60-79	1	0	1	3	6	5	5	21
80-99	1	3	0	1	0	1	1	7
100-119	0	1	0	0	2	1	2	6
120-139	0	0	0	0	1	0	1	2
140+	1	0	1	0	0	0	0	2
Total, cases	12	15	10	14	14	12	34	111
Average hypertrophy, %	51.2	41.1	48.1	36.2	65.5	56.8	40.3	46.8

TABLE 4.—THE DISTRIBUTION ACCORDING TO SEX AND THE MINIMAL DURATION OF HYPERTENSION

Minimal duration, years	Males		Females		Total, cases
	Cases	%	Cases	%	
0-4	32	49.2	10	21.7	42
5-9	12	18.5	8	17.4	20
10-14	8	12.3	8	17.4	16
15-19	7	10.8	7	15.2	14
20-24	4	6.1	4	8.7	8
25+	2	3.1	9	19.6	11
Total	65	100.0	46	100.0	111

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# A STUDY OF THE COMPARATIVE VALUE OF TETRAETHYLAMMONIUM BROMIDE AND DIAGNOSTIC SPINAL ANESTHESIA IN THE SELECTION OF HYPERTENSIVE PERSONS FOR SYMPATHECTOMY

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SOME, but not all, persons with hypertension are benefited by extensive sympathectomy and ganglionectomy. However, there are as yet no reliable methods or tests by which one may with certainty distinguish those whose blood pressures will be favorably influenced from those whose pressure will not be significantly changed. Numerous rules and tests have been suggested for selecting persons suitable for operation. Smithwick<sup>5</sup> has laid down useful criteria which he has developed on the basis of his extensive experience. Essentially, these tests depend upon determining the effect on the blood pressure of sedation or sleep, which is assumed to minimize stimuli which affect the nervous system; or the effect of some method, such as the cold pressor test, which increases stimulation of the nervous system. By these methods one attempts to assess the neurogenic component of hypertension. These methods have not proved very satisfactory in the selection of patients for operation.

More recently 2 new tests have been proposed: the effect of tetraethylammonium ion and the effect of diagnostic spinal anesthesia. Each appears to have some merit but neither offers as yet the final solution.

Lyons<sup>2</sup> has proposed the use of the

tetraethylammonium ion as a preoperative test for selecting hypertensive persons for sympathectomy and ganglionectomy. This test is based on the temporary blockade of the sympathetic ganglia so that the vaso-constricting action of the sympathetic nerves is abolished. Page<sup>1</sup>, on the other hand, was unable to confirm this observation. He reported 12 cases. Five of his patients (Nos. 1, 4, 12, 14 and 15), as judged by our criteria, had no significant drop in diastolic pressure following the administration of tetraethylammonium chloride. Seven of his patients did have a significant drop in blood pressure following the administration of the drug. Two of these 7 patients were favorably influenced by lumbo-dorsal sympathectomy and ganglionectomy. Objections may be raised against his conclusions on the basis that the operative procedure was not sufficiently extensive.

Russek and his associates<sup>4</sup> have commented favorably on the effect of epidural anesthesia on the blood pressure as a test for the selection of hypertensive persons suitable for sympathectomy and ganglionectomy.

Because of the fragmentary work which had been done on the use of the tetraethylammonium ion and epidural anesthesia as tests for the selection of



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ties which might further lower the blood pressure. Methods and Materials. During 1947 and the first 2 months of 1948, 29 persons were admitted into Temple University Hospital for possible sympathectomy. Of these, 28 were tested for the blood pressure lowering effect of diagnostic spinal anesthesia. Twenty-five were tested for the blood pressure lowering effect of tetraethylammonium bromide. Of these in cases, both tests were applied. Of these in basis of this report.

The non-operative or incomplete cases include the following: 2 refused or were re-fused surgery. Two died after the first stage, 1 of a stroke and the other of heart failure. The first was a satisfactory risk who failed to react from anesthesia and at autopsy revealed necrosis of the right frontal parietal and temporal lobes. The second had malignant hypertension and was known to be an extremely poor operative risk. One refused the second stage. Two are to be done.

paralysis and relaxation and the consequent pooling of blood in the extrem-

motor block. This prevents muscular obtained without the production of a thesia and autonomic block are easily tionally injected, sensory levels of anes- easier and, with dilute solutions of frac- School of Medicine, it is technically ion of Dr. Curtiss B. Hickcox, Professor of Anesthesiology at Temple University dural anesthesia because, in the opin- esthesia was used in preference to epi- ganglionectomy. Diagnostic spinal an- thoracolumbar sympathectomy and with that obtained by an extensive compare the effect of both of them effect of these two methods and to compare the blood pressure lowering hypertensive persons for sympathectomy, we thought it worth lowering blood pressure.

TABLE 1.-BLOOD PRESSURE DATA ON 24 HYPERTENSIVES:  
FALL IN THE DIASTOLIC PRESSURE (A-C) (B-C)  
FALL IN THE SYSTOLIC PRESSURE (A-C) (B-C)  
(A) AVERAGE OF 10 SUPINE READINGS; (B) ONE SUPINE READING AFTER INJECTION OF 500 MG. OF TETRAETHYLAMMONIUM BROMIDE; (C) LOWEST SUPINE READING AFTER INJECTION

NAME AND CASE NUMBER	AGE	SEX	AVERAGE BLOOD PRESSURE (10 READINGS)	SUPINE	PREINJECTION BLOOD PRESSURE	POST INJECTION BLOOD PRESSURE	FALL IN THE DIASTOLIC PRESSURE (A-C) (B-C)	FALL IN THE SYSTOLIC PRESSURE (A-C) (B-C)
1 E.C.	33	F	226/151		240/150	140/100	51	100
2 P.B.	39	F	159/117		150/130	134/94	22	60
7 C.K.	26	F	191/120		192/130	148/108	11	44
8 R.D.	46	F	179/107		200/112	136/92	28	20
9 J.H.	41	M	178/119		180/110	140/90	17	20
10 M.R.	34	F	196/143		220/164	138/104	50	36
11 D.E.	24	F	156/113		184/120	110/70	50	36
12 A.V.	32	F	171/104		200/110	124/82	22	60
13 J.D.	41	F	172/104		168/102	124/82	15	44
14 M.K.	43	F	208/132		240/140	160/88	51	100
15 M.B.	49	M	193/135		200/130	110/60	22	60
16 A.S.	26	M	192/127		242/148	130/100	11	44
17 M.B.	31	F	203/128		170/110	104/66	22	60
18 C.O.	50	F	164/105		154/100	110/70	50	36
19 E.M.	41	F	222/127		222/124	190/110	22	60
21 C.P.	53	F	201/133		230/140	128/88	50	36
22 B.Y.	38	M	224/142		210/168	126/88	22	60
23 M.V.	39	F	215/133		240/120	182/110	50	36
25 C.L.	48	F	221/140		170/110	128/84	22	60
26 C.C.	48	M	203/141		154/99	108/68	50	36
27 C.G.	47	F	154/99		170/110	128/84	22	60
28 M.H.	40	F	171/98		240/120	182/110	50	36
29 W.S.	40	F	221/140		240/120	182/110	50	36

Two were tested following Smithwick operations done in 1945.

The remaining 20 were submitted to an extensive transpleural thoracolumbar sympathectomy bilaterally. Ganglia from the second thoracic to the second lumbar, inclusive, were resected along with the intervening chains and the splanchnic nerves down to but not including the coeliac ganglia. In 4 or 5 patients, the second and third thoracic or the second lumbar zones were not resected on one or the other side due to urgency for termination of the operation or the fact that the preoperative ascending diagnostic spinal test had indicated a drop of the blood pressure to normal at the level of the sixth thoracic segment or below. One had the malignant phase of hypertension, 13 had essential hypertension and 6 had mild to moderate impairment of renal function.

Blood pressure readings were taken in the supine, sitting and standing positions preop-

eratively and postoperatively to determine the effects of posture before and after operation, but only supine readings were taken following the administration of tetraethylammonium bromide and the use of diagnostic spinal anesthesia. All patients were in the hospital for at least one week and frequently for several weeks before operation. Blood pressure readings were taken twice daily by a trained nurse, checked frequently by a resident and taken repeatedly by at least one of us. Control values represent the average of the last 10 readings preoperatively. The postoperative values represent the average of the last 10 readings taken before discharge from the hospital. The blood pressure immediately preceding diagnostic spinal anesthesia and that preceding the administration of tetraethylammonium bromide are also given.

With the patient in bed, 500 mg. of tetraethylammonium bromide were injected intra-

TABLE 2.—BLOOD PRESSURE DATA ON 29 HYPERTENSIVES:

(A) AVERAGE OF 10 SUPINE READINGS; (B) ONE SUPINE READING IMMEDIATELY BEFORE, AND  
(C) LOWEST SUPINE READING AFTER DIAGNOSTIC SPINAL ANESTHESIA

NAME AND CASE NUMBER	AGE	SEX	(A) AVERAGE BLOOD PRESSURE (10 READINGS) SUPINE	(B) CONTROL BLOOD PRESSURE PRIOR TO SPINAL SUPINE	(C) MAXIMUM FALL IN BLOOD PRESSURE	FALL IN THE SYSTOLIC PRESSURE		FALL IN THE DIASTOLIC PRESSURE	
						(A-B)	(A-C)	(A-B)	(A-C)
1 E.G.	33	F	226/151	240/140	240/155	+ 14	0	+ 11	+ 15
2 P.B.	39	F	199/144	220/120	100/70	99	120	74	50
3 H.L.	28	F	215/117	200/110	150/80	65	50	37	30
4 A.L.	44	M	180/118	200/120	140/90	40	60	28	30
5 M.V.	42	F	195/112	230/130	90/60	105	140	52	70
6 M.S.	55	F	195/107	170/100	100/60	95	70	47	40
7 C.K.	26	F	159/117	205/110	120/75	39	85	42	35
8 R.D.	46	F	191/120	230/120	130/90	61	100	30	30
9 J.H.	41	M	179/107	160/105	108/74	71	52	33	31
11 D.E.	24	F	196/143	160/105	110/70	86	50	73	35
12 A.V.	32	F	156/113	160/120	110/80	46	50	33	40
13 J.D.	41	F	171/104	200/110	110/70	61	90	34	40
14 M.K.	43	F	172/104	194/110	125/85	47	69	19	25
15 M.B.	49	M	208/132	220/140	120/95	88	100	36	44
16 A.S.	26	M	193/135	220/140	130/110	63	90	25	30
17 M.B.	45	M	219/130	210/120	130/98	89	80	32	22
18 C.O.	31	F	192/127	184/120	130/80	62	54	47	40
19 E.M.	50	F	203/128	220/130	110/80	93	110	48	50
20 F.S.	40	F	187/118	200/140	140/92	47	60	26	48
21 C.P.	41	F	164/105	170/108	100/60	64	70	45	48
22 B.Y.	53	F	222/127	220/130	160/100	62	60	27	30
23 M.V.	38	M	201/133	230/150	160/110	41	70	23	40
24 I.K.	39	F	224/142	212/150	104/60	120	108	62	90
25 C.L.	48	F	215/133	240/130	160/100	55	80	33	30
26 C.G.	48	M	221/140	236/150	190/130	31	48	10	20
27 C.G.	33	M	203/141	190/144	170/118	33	27	23	26
28 M.H.	47	F	154/99	210/120	120/80	34	97	19	40
29 M.S.	40	F	171/98	190/90	150/60	21	47	8	0

venously and the blood pressure taken every minute for 5 minutes and then every 5 minutes until it reached its original level. The maximum drop in blood pressure is recorded (Table 1).

Diagnostic spinal anesthesia was performed by or under the direction of Dr. Hickcox. Continuous fractional spinal anesthesia was employed, with 0.2 to 2% of solution of procaine hydrochloride. The average dilution was 0.5%. If no reaction was obtained, the strength was decreased. The average fractional dose was 25 to 30 mg. of procaine hydrochloride. The pulse and blood pressure were checked at each sensory level for 4 to 5 minutes. Anesthesia was carried cephalad until the recumbent blood pressure dropped to normal and the level noted. In several, this required ascent to thoracic one and in 2 instances there was no decrease. The results are recorded in Table 2.

The operations were performed by one of us (WEB) or his associates. All operations, as previously described, consisted of extensive thoracolumbar sympathectomy and ganglionectomy. The postoperative results are recorded in Table 3.

**Results. (a) EFFECTS OF TETRAETHYL-AMMONIUM BROMIDE.** The pharma-

cologic effects of the tetraethylammonium ion have been amply described previously and will not be repeated here. Two interesting phenomena not previously described or stressed were observed. One was a rise in blood pressure following the fall; this occurred in 3 of 20 cases, and on one occasion was 50 mm. of mercury higher than the pre-test level. This effect tended to occur about one-half hour after the maximum fall and lasted a few minutes. In the one with 50 mm. of mercury rise, a transient hemiparesis occurred. The other phenomenon was an apparent tolerance to the drug. In the beginning, we tried to treat our hypertensive patients with repeated injections of the drug. The injections were given at 4 hour intervals. There was less blood pressure lowering effect and the duration of the effect was shorter with succeeding doses. Only 3 patients were so tested and all 3 re-

TABLE 3.—BLOOD PRESSURE DATA ON 20 HYPERTENSIVES:

(A) AVERAGE OF 10 SUPINE PRE-OPERATIVE READINGS; (B) AVERAGE OF 10 SUPINE POST OPERATIVE READINGS FOLLOWING BILATERAL THORACOLUMBAR SYMPATHECTOMY

NAME AND CASE NUMBER	AGE	SEX	(A) AVERAGE PRE-OP BLOOD PRESSURE (10 READINGS) SUPINE	(B) AVERAGE MAXIMUM FALL IN BLOOD PRESSURE (10 READINGS) SUPINE	FALL IN THE SYSTOLIC BLOOD PRESSURE (A-B)	FALL IN THE DIASTOLIC BLOOD PRESSURE (A-B)
1 E.G.	33	F	226/151	154/106	72	45
2 P.B.	39	F	199/144	157/111	42	33
3 L.H.	28	F	215/117	185/109	30	8
4 A.L.	44	M	180/118	153/103	27	15
5 M.C.	42	F	195/112	146/92	49	20
6 M.S.	55	F	195/107	182/103	13	4
7 C.K.	26	F	159/117	162/112	3	5
8 M.D.	46	F	191/120	170/113	21	7
9 J.H.	41	M	179/107	149/97	30	10
10 M.R.	34	F	178/119	119/78	59	41
11 D.E.	24	F	196/143	206/146	10	3
12 A.V.	32	F	156/113	117/73	39	40
13 J.D.	41	F	171/104	135/93	36	11
14 M.K.	43	F	172/104	160/107	12	3
15 M.B.	49	M	208/132	139/91	69	41
16 A.S.	26	M	193/135	99/74	94	61
17 M.B.	45	M	219/130	222/149	3	19
18 C.O.	31	F	192/127	191/135	1	8
19 E.M.	50	F	203/128	138/85	65	43
20 F.S.	40	F	187/118	136/89	51	29

sponded to repeated injections of tetraethylammonium bromide in this way. These responses may represent inconstant effects of the drug or variable nervous tone in the patient rather than true tolerance. More observations are necessary to determine the nature of response to repeated injections at frequent intervals.

A significant drop in blood pressure was regarded as one in which the diastolic pressure fell 20 mm. of mercury or more compared to the average diastolic pressure. The drop in diastolic

pressure compared to the pressure immediately preceding the test is also given, so that comparisons of the two drops can be made in order to determine what if any significance this drop has.

Eighteen of 24 had a significant drop in diastolic pressure following the administration of tetraethylammonium bromide. Eleven of 24 had a drop to normotensive levels. The nature, degree, duration, etiology of the hypertension or the sex had no relation to

TABLE 4.—DATA ON FALL OF DIASTOLIC BLOOD PRESSURE IN 29 HYPERTENSIVES:

EFFECTS PRODUCED BY (A) OPERATION, (B) DIAGNOSTIC SPINAL ANESTHESIA, AND (C) AFTER TETRAETHYLAMMONIUM BROMIDE INJECTION. (FIGURES REPRESENT FALL OF BLOOD PRESSURE IN MM/HG. A DASH SIGNIFIES THAT TEST OR OPERATION WAS NOT DONE).

NAME AND CASE NUMBER	AGE	SEX	(A) AFTER OPERATION	(B) AFTER DIAGNOSTIC SPINAL ANESTHESIA		(C) AFTER TETRAETHYLAMMONIUM BROMIDE INJECTION	
				(B 1) COMPARED WITH AVERAGE OF 10 SUPINE READINGS	(B 2) COMPARED WITH A SUPINE READING JUST BEFORE ANESTHESIA	(C 1) COMPARED WITH AVERAGE OF 10 SUPINE READINGS	(C 2) COMPARED WITH A SUPINE READING JUST BEFORE THE DRUG INJECTION
1 E.G.	33	F	45	+ 11	+ 15	51	50
2 P.B.	39	F	33	74	50	50	36
3 H.L.	28	F	8	37	30	—	—
4 A.L.	44	M	15	28	30	—	—
5 M.C.	42	F	20	52	70	—	—
6 M.S.	55	F	4	47	40	—	—
7 C.K.	26	F	5	42	35	42	22
8 R.D.	46	F	7	30	30	28	20
9 J.H.	41	M	10	33	31	17	20
10 M.R.	34	F	41	—	—	15	60
11 D.E.	24	F	3	73	35	3	24
12 A.V.	32	F	40	33	40	49	56
13 J.D.	41	F	11	34	40	34	40
14 M.K.	43	F	3	19	25	22	20
15 M.B.	49	M	41	36	34	44	52
16 A.S.	26	M	61	25	30	75	70
17 M.B.	45	M	19	32	22	0	18
18 C.O.	31	F	8	47	40	27	20
19 E.M.	50	F	43	48	50	62	44
20 F.S.	40	F	29	26	48	—	—
21 C.P.	41	F	—	45	48	35	30
22 B.Y.	53	F	—	27	30	17	14
23 M.V.	39	M	—	23	40	45	27
24 I.K.	39	F	—	82	90	28	64
25 C.L.	48	F	—	33	30	23	30
26 C.G.	48	M	—	10	30	20	0
27 C.G.	33	M	—	23	26	37	20
28 M.H.	47	F	—	19	40	15	26
29 V.S.	40	F	—	8	0	30	32

done) and operation (when performed). It is generally recognized that during the first year after operation there is a gradual rise in pressure which is said to average somewhat less than 15 mm. of mercury obtained before operative figures left the hospital. Judged by some of our earlier patients, our results one year after operation will show less of a drop than as reported now. It was for this reason that 20 mm. of mercury was taken as the minimum significant drop. If the results are reported as a percentage of the diastolic pressure and 15% is regarded as significant, our findings are substantially the same.

Our findings verify the contention of Page and fail to verify the report of Lyons. It can be seen that neither a significant response to tetraethylammonium bromide nor to diagnostic spinal anesthesia can be used to predict a satisfactory response to operation. Indeed, even a significant response to both procedures will be successful in lowering the diastolic pressure. The wide-spread effect of tetraethylammonium bromide on both the sympathetic and parasympathetic systems and the constancy of its effect on the same individual are probably some reasons for its failure as a reliable test to predict a satisfactory outcome from surgery. The frequency with which drops in pressure that additional mechanisms are in action which are not present after operation. A comparison of the blood pressure and tetraethylammonium half the lowering effects of spinal anesthesia shows that in more than half the patients both procedures produced good results.

# (b) EFFECTS OF DIAGNOSTIC SPINAL ANESTHESIA. Twenty-three of 28 had a significant drop in diastolic pressure following spinal anesthesia. Twenty-one of 28 had a drop to normotensive levels. Again, the nature, degree, duration, etiology of the hypertension or the sex had no relation to the presence or absence of a significant drop in diastolic pressure.

Of the 28 tested with diagnostic spinal anesthesia, 19 were operated upon. Eight had significant drops in pressure postoperatively, and 10 had poor results. Of the 8 good results, 7 had good responses to diagnostic spinal anesthesia and 1 had a poor response. Of the 10 bad results, 9 had good responses and 1 had a poor response. Twenty-three patients were tested with both tetraethylammonium bromide and good responses to spinal anesthesia and poor responses to tetraethylammonium bromide. Six had good responses to both methods. Fourteen had good responses to tetraethylammonium bromide, and 3 had poor responses to spinal anesthesia. Of the 14 patients subjected to operation, 8 were obtained good results, 4 were poor results. In Table 4 there are recorded the several effects produced in our 29 patients by both tests (when performed).

Discussion. In Table 4 there are recorded the several effects produced in our 29 patients by both tests (when performed). It is generally recognized that during the first year after operation there is a gradual rise in pressure which is said to average somewhat less than 15 mm. of mercury obtained before operative figures left the hospital. Judged by some of our earlier patients, our results one year after operation will show less of a drop than as reported now. It was for this reason that 20 mm. of mercury was taken as the minimum significant drop. If the results are reported as a percentage of the diastolic pressure and 15% is regarded as significant, our findings are substantially the same.

significant changes in pressure. In a little less than half, one procedure produced an adequate response and the other did not. In some instances, spinal anesthesia was superior to tetraethylammonium bromide in its blood pressure lowering effects and in others the reverse was true. Likewise, the degree of reaction was frequently different. This indicates that these procedures affect different factors which together are responsible for the maintenance of blood pressure.

More recently, Lyons<sup>3</sup>, on the basis of more evidence, has come to a conclusion similar to ours so far as the tetraethylammonium ion is concerned. He states that "a good response to the drug does not necessarily indicate that a successful result from splanchnicotomy can be expected." He rather cautiously suggests that the failure of response to the drug may be used as a test to exclude hypertensive persons for splanchnicotomy. The same thought with regard to epidural anesthesia is implied in the work of Russek.

It can be seen from our findings that one patient with a poor response to diagnostic spinal anesthesia and one patient with a poor response to tetraethylammonium bromide had excellent results following operation. Furthermore, the blood pressure of the patient varies from time to time and the response of the patient to tetraethylammonium bromide varies from time to time. Two extreme conditions may be obtained: The pre-test blood pressure may be higher or lower than the average blood pressure. In the first instance, a marked response to the drug may occur without having the resultant pressure lower than the average pressure. In the second instance, no response from the drug may occur because the pressure has already dropped considerably compared to the average pressure. This is seen in Cases 17 and 26. Furthermore, because of the

great variability of the pressure, one is never certain of the true average pressure from a short period of observation. Lastly, the neutralizing effect of an increase in adrenalin cannot be excluded. For these reasons, with the data available at the present time, we feel it unwise to exclude patients from operation simply on the basis of poor responses to those two tests.

Because of the failure of these tests to predict accurately the outcome of surgery we re-examined our clinical findings to see whether one of the usual rules given for selection of patients for sympathectomy could have been applied successfully. Our group was relatively young. No patient was above the age of 50. Two out of 5 males and 7 out of 15 females obtained significant postoperative decrease in diastolic pressure. The pulse pressure was less than 19 plus one-half the diastolic pressure in all persons whose operation was successful (Types I and II of Smithwick). However, 7 persons whose operation was unsuccessful had similar pulse pressures. Therefore this criterion was no more reliable.

**Summary and Conclusions.** 1. Of 29 hypertensive persons admitted for possible sympathectomy and ganglionectomy, 28 were tested for the blood pressure lowering effect of fractional spinal anesthesia, 24 were tested for the blood pressure lowering effect of tetraethylammonium bromide and 20 were subjected to an extensive bilateral thoracolumbar sympathectomy and ganglionectomy.

2. The inconstancy of the blood pressure lowering effect of tetraethylammonium bromide is stressed.

3. Eighteen of 24 had good responses to tetraethylammonium bromide. Twenty-three of 28 had good responses to diagnostic spinal anesthesia. Fourteen of 23 had good responses to both tests.

4. Seven good responses to sympath-

ectomy had 6 good responses and 1 bad response to tetraethylammonium bromide. Eight bad results of operation had 4 good and 4 bad responses to the drug.

5. Eight good results of sympathectomy had 7 good responses and 1 bad response to diagnostic spinal anesthesia. Ten bad results of operation had 9 good responses and 1 bad response to diagnostic spinal anesthesia.

6. Eight good responses to both tetraethylammonium bromide and spinal anesthesia obtained 4 good results and 4 poor results from operation.

7. Good responses from tetraethylammonium bromide or diagnostic spinal anesthesia or from both can not be used as reliable tests to predict good results from sympathectomy.

8. With our present data, it is advised that sympathectomy should not be withheld on the basis of insignificant responses to tetraethylammonium bromide or spinal anesthesia.

9. A re-examination of our clinical data fails to reveal any method, including the pulse pressure, which will predict accurately the blood pressure lowering effect of sympathectomy.

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# ELECTROCARDIOGRAPHIC AND CLINICAL STUDIES ON THE ACTION OF ERGOTAMINE TARTRATE AND DIHYDRO-ERGOTAMINE 45

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IN recent years preparations of ergotamine have been used rather widely in cardiovascular research and have been advocated for the treatment of various conditions. Thus, they have been administered for the treatment of hypertension<sup>10</sup> and paroxysmal tachycardia.<sup>4</sup> Moreover, ergotamine has been recommended as a diagnostic test in subclinical rheumatic fever,<sup>18</sup> and on the basis of animal experimentation, it has been suggested that the administration of ergotamine may reduce the immediate mortality in acute coronary occlusion.<sup>9</sup>

The view has been expressed that a high sympathetic tonus is responsible for the abnormal T waves often seen when individuals assume the erect posture. This opinion is based on the observation that the intravenous injection of ergotamine tartrate prevents the appearance of these electrocardiographic changes.<sup>11</sup> Likewise, alterations of the T waves in the chest leads have been ascribed to "functional" influences produced by an abnormal vagus or sympathetic tonus. Following the intravenous injection of 0.5 mg. of ergotamine tartrate these alterations of the T waves disappeared and were explained by excessive adrenergic preponderance.<sup>7,11,15,17,19</sup>

Finally during the anoxemia test abnormal electrocardiographic changes

occasionally occur in patients with healthy hearts. If the anoxemia test is repeated after the administration of ergotamine, these changes were said to be absent; this permits one to differentiate between the alterations due to organic coronary disease and those found in patients with normal coronary arteries.<sup>1,3</sup>

In a previous study it was demonstrated that changes in the electrocardiogram which occur on standing are occasionally but not always prevented by ergotamine.<sup>13</sup> Deep inversion of the T waves may appear on assuming the erect posture even after the injection of ergotamine.

It seemed to us that if ergotamine preparations could change the repolarization process and alter the functionally inverted T waves by their sympathicolytic action they should also have a similar effect in organic heart disease and occasionally lead to a normalization of organically inverted T waves.

**Method of study and material.** Nineteen patients who suffered from organic heart disease and who showed inverted T waves in leads I and CF<sub>2</sub> were studied. These T wave changes were caused by left ventricular hypertrophy in luetic heart disease, rheumatic heart disease, hypertension or by an old myocardial infarction.

All electrocardiograms were obtained with the patient in the supine position. The



patient received an intravenous injection of 0.5 mg. of either ergotamine tartrate or dihydro-ergotamine 45\* after the recording of the control electrocardiogram. Electrocardiograms were then taken 15, 30 and 45 minutes after the injection.

**Results.** Seven of the 19 patients developed significant alterations of the T waves after the administration of ergotamine. As Table 1 shows, the inverted T<sub>1</sub> became upright in 4 patients and the inverted T waves in Lead CF<sub>5</sub> became upright in 3 instances. In 2 patients the originally inverted T waves in Lead I became more inverted and a similar phenomenon occurred twice in Lead CF<sub>5</sub>.

Figure 1 shows the electrocardiogram of a 59 year-old male patient who had a history of hypertension and cardiac decompensation for a number of years. The control electrocardio-

gram (Fig. 1a) shows a slight left axis deviation, some slurring of the QRS complexes and flat T waves in Leads I and CF<sub>5</sub>. Fifteen minutes after the injection of ergotamine tartrate the T waves have become higher (Fig. 1b) and they are almost normal 45 minutes after the injection (Fig. 1c).

Figure 2 shows the electrocardiogram of a 56 year-old man with a blood pressure of 210/130 mm. Hg. The heart was markedly enlarged and there was evidence of right and left ventricular failure. Figure 2a shows Lead I and CF<sub>5</sub> with a depression of the RS-T segments and inverted T waves, as is often seen in long lasting hypertension with left ventricular hypertrophy. Fifteen minutes after the injection of 0.5 mg. of ergotamine tartrate there are no significant changes in Lead I but positive T waves appear in Lead CF<sub>5</sub>.

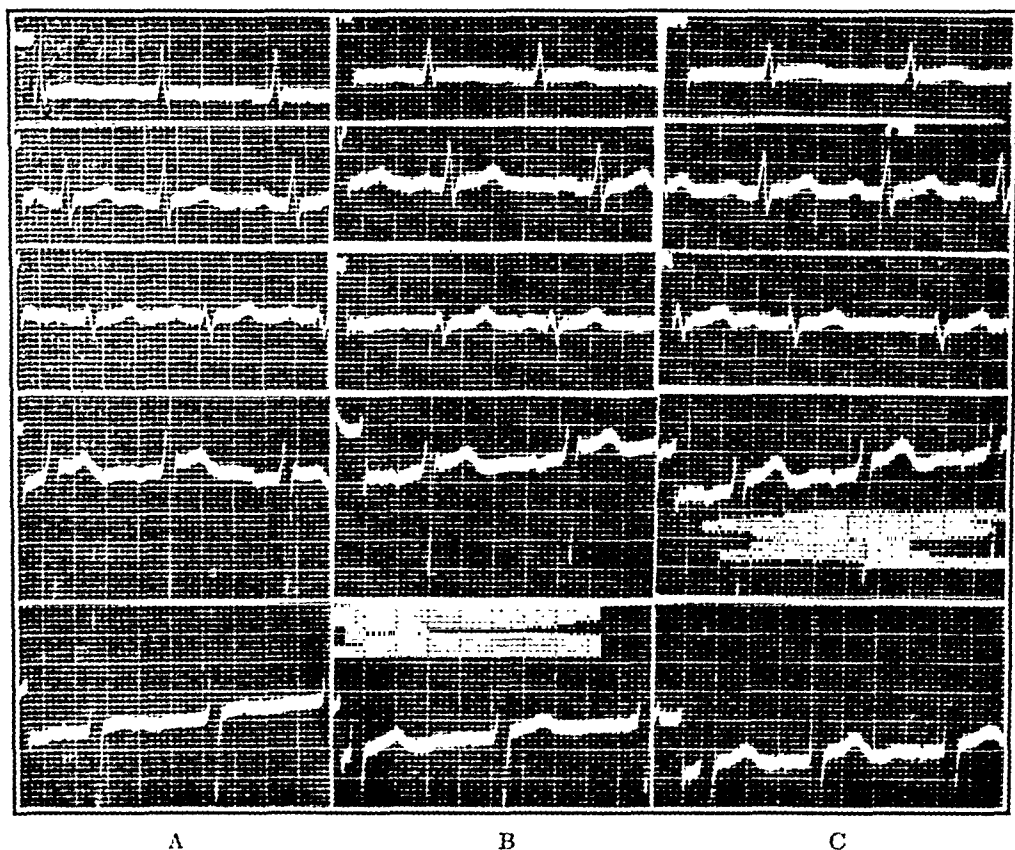


Fig. 1.—Fig. 1a shows the electrocardiogram before, and Fig. 1b 15 minutes after the intravenous injection of ergotamine tartrate. Fig. 1c was obtained 45 minutes after the injection. The 2 bottom tracings are Leads CF<sub>2</sub> and CF<sub>5</sub>.

\* Our thanks are due to Dr. Henze of the Sandoz Company for the supply of this drug.

(Fig. 2b). These changes still persist 45 minutes after the injection (Fig. 2c).

It is evident from these results that not only functionally inverted T waves but also T waves which are inverted because of organic heart disease may become upright following administration of ergotamine.

*Anginal pain following ergotamine.* Five of the patients developed severe anginal pain after the injection of er-

terior wall of the left ventricle. Fifteen (Fig. 3b) and 45 minutes (Fig. 3c) after the intravenous injection of dihydro-ergotamine 45 the T waves were distinctly positive in both Lead I and Lead CF<sub>5</sub>.

Within 5 minutes after the injection the patient complained of excruciating pain which was similar to the angina he experienced on effort. This present pain however was more severe. The pain persisted for 10 hours and because of this and marked sweating, retching and vomit-

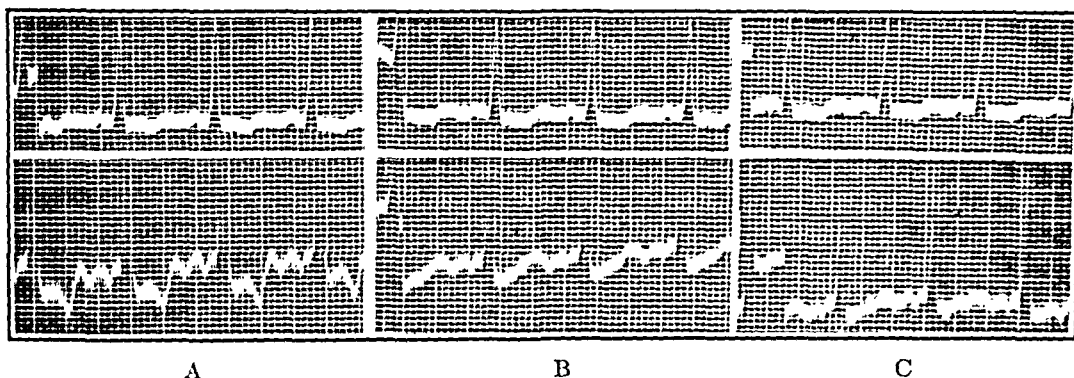


Fig. 2.—Fig. 2a shows Lead I and Lead CF<sub>5</sub> before, and Fig. 2b and 2c, 15 and 45 minutes after the intravenous injection of ergotamine tartrate.

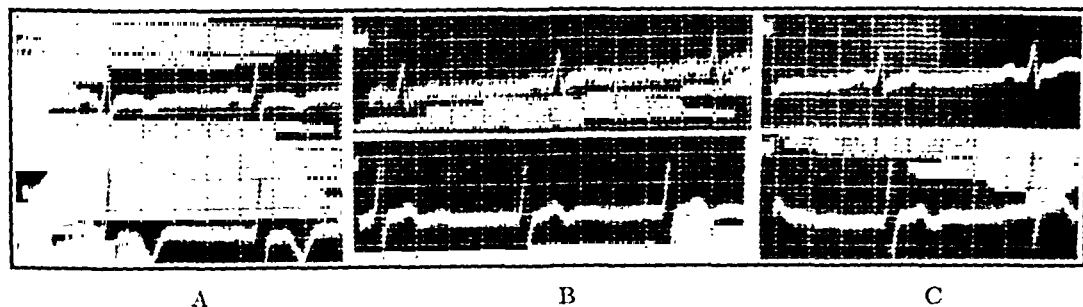


Fig. 3.—Fig. 3a was recorded before the intravenous injection of dihydro-ergotamine 45 and Figs. 3b and 3c were obtained respectively 15 and 45 minutes after the injection.

gotamine and one of these patients died during the attack.

**Case Reports:** *Case 1.* A 75 year-old male had a history of coronary thrombosis 2 years before admission. The patient was hospitalized because of angina on effort which had become progressively worse. Figure 3a shows the electrocardiogram (Leads I and CF<sub>5</sub>) taken before the administration of ergotamine. It shows normal RS-T segments and deeply inverted T waves. These findings are consistent with an old infarction of the

ing a fresh coronary thrombosis was suspected. The subsequent findings did not show evidence of a new myocardial infarction and an electrocardiogram taken 4 hours after the onset of the pain but while pain still persisted, showed a pattern similar to that in Figure 3a. Subsequent electrocardiograms revealed no further changes.

*Case 2.* A 75 year-old male had a hypertension for many years and was admitted to the hospital because of left ventricular failure. The electrocardiogram showed depression of the RS-T segments

and low T waves in Leads I and  $CF_5$ . The other leads were normal. Fifteen minutes after the injection of dihydro-ergotamine 45 the T waves in the apical chest lead became deeply inverted. The inversion increased during the next 15 minutes but subsided somewhat after 45 minutes. The T waves in Lead I were isoelectric 30 and 45 minutes after the injection. No changes developed in the other leads.

This patient developed severe substernal pain, profuse sweating, nausea and tingling in the extremities within 10 minutes after the injection. The substernal pain persisted for 2 hours.

*Case 3.* A 65 year-old male who was admitted because of left ventricular failure and with a blood pressure of 190/100. The electrocardiogram showed a typical pattern of left ventricular strain. This

patient developed substernal pain 10 minutes after the injection of 0.5 mg. of ergotamine tartrate and this pain persisted for one hour. Electrocardiograms taken 15, 30 and 45 minutes after the injection showed no change from his control tracing.

*Case 4.* A 63 year-old male was admitted to the hospital for left ventricular failure with a blood pressure of 220/130. He also showed an electrocardiographic pattern of left ventricular strain. Anginal pain occurred 15 minutes after the injection of ergotamine tartrate and lasted for 45 minutes. No alterations occurred in the electrocardiogram.

*Case 5.* Figure 4 shows the tracings from a 58 year-old male with syphilitic heart disease, incompetency of the aortic valves and stenosis of the coronary ostia. As this patient died following the injection of 0.5 mg. of dihydro-ergotamine 45,

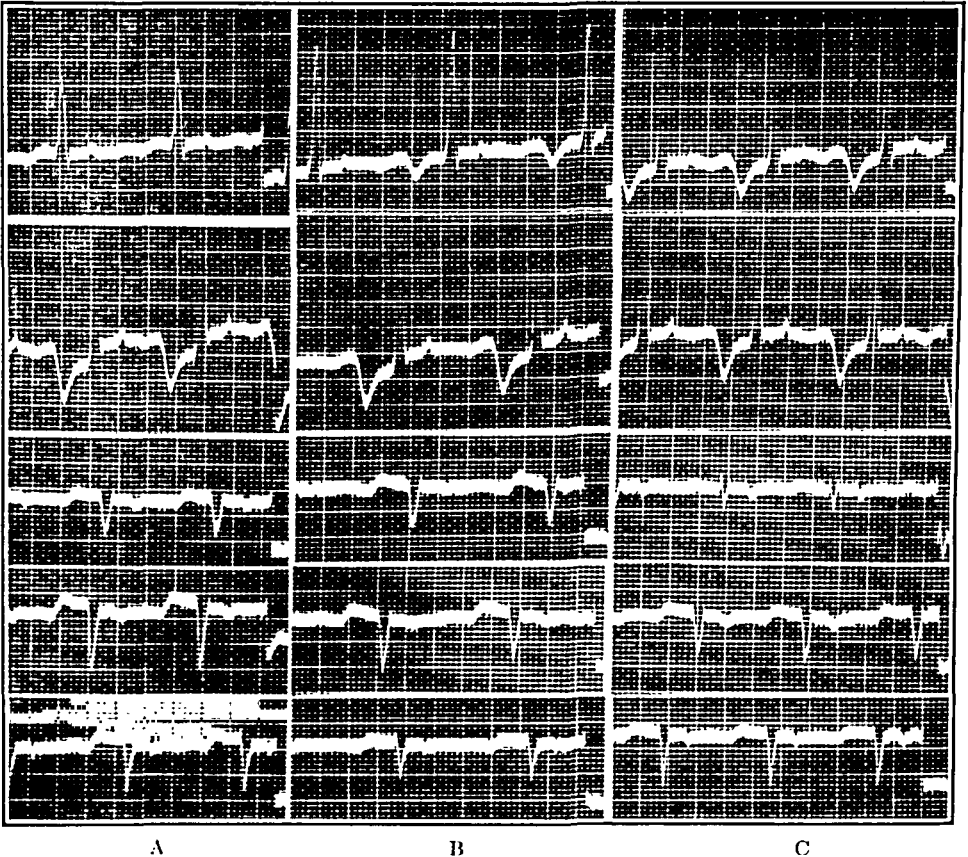


Fig. 4.—Fig. 4a shows the 3 standard leads and Leads  $CF_2$  and  $CF_5$  before the intravenous injection of dihydro-ergotamine. Fig. 4b was taken 15 minutes after the injection and Fig. 4c 30 minutes later.

the observations will be reported in greater detail.

The patient was in good health until 2 years before admission when weakness, shortness of breath, malleolar edema and retrosternal pain on exertion developed. For the past 2 months substernal pain appeared on the slightest exertion but subsided with rest. Several years ago the patient was told that he had a hypertension. He denied lues but admitted to an urethral stricture. The family history revealed that 2 brothers had died from heart disease and the mother from a stroke.

The patient was in no acute distress on admission. The eyes reacted poorly to light; there was ataxia of the hands and the legs, and diminished vibratory sense over the right lower extremity. The carotid pulsations were forceful and equal and the cervical veins were distended. There was a water hammer pulse and the blood pressure was 150/45. The apex was in the 6th intercostal space outside of the mid-clavicular line; the heart of an aortic shape with a marked dilatation of the left ventricle and a widening of the ascending aorta. Systolic and diastolic murmurs were heard over the right second intercostal space. There was some fluid in the right pleural sinus. The liver was markedly enlarged and there was pitting edema of the ankles.

The patient improved with therapy. On the 6th day after admission at 10 A.M., the patient was given an intravenous injection of 0.5 mg. of dihydro-ergotamine 45. Ten minutes later he complained of severe substernal pain, was very nauseated, dyspneic and insisted upon sitting up in bed. At noon the pain still persisted and it was noted that the patient was incoherent, cold, clammy and vomiting. At 4 P.M. pain was still present, the cardiac rate was 128 per minute with many extrasystoles. The respiration was rapid and irregular. The blood pressure which had been 160/50 one half-hour previously was now 110/50. At 8 P. M. the pain still persisted, the blood pressure was 115/55 and the heart rate had slowed to 84 per minute. The patient seemed more alert. He died at 9:50 P.M.

The autopsy revealed syphilitic aortitis with aortic insufficiency, atheromatosis,

narrowing of both coronary orifices and coronary sclerosis. The left ventricle was hypertrophied and myocardial fibrosis was present in the apical area. Pulmonary edema and chronic congestion of the liver existed.

The electrocardiogram taken before the injection (Fig. 4a) showed slurring but no widening of the QRS complexes and inverted T waves in the limb leads. Only equivocal modifications of the T waves appeared 15 minutes after the injection (Fig. 4b). These were accompanied by slight changes of the QRS complex. In the tracing taken 45 minutes after the injection, the inversion of the T waves in the limb leads was more marked and the T waves in Lead CF<sub>5</sub> became abnormal (Fig. 4c).

**Discussion.** This investigation shows that alterations of the electrocardiogram which are due to organic heart disease may disappear with the administration of ergotamine preparations. As Table 1 indicates, this normalization of the inverted T waves in patients with organic heart disease is seen in many different conditions and not only in patients with hypertension.

Preparations of ergotamine do not produce a consistent alteration of organically inverted T waves. Table 1 shows that in 12 patients no changes of the T waves occurred. Of the 7 patients who developed significant changes, in 2 the inverted T waves became even more inverted and in 5 normalization of the previously inverted T waves occurred. Further investigation will be necessary to explain these differences of response.

All of the changes which occur in the electrocardiogram after the administration of ergotamine preparations can not be attributed to the sympatholytic properties of this drug. It has been shown that the accelerans mechanism in the heart is not paralyzed by ergotamine even when huge doses are given.<sup>12</sup> The effect of the drug on the blood pressure in man is variable and often slight. A direct vasoconstricting action

of the coronary arteries is probable.<sup>14</sup>

Five of the patients studied developed severe substernal pain after the injections of ergotamine and one of these patients died. The electrocardiographic changes did not parallel the symptom of angina. Two of the patients who had anginal pain did not

Anginal pain and cardiac complications following the administration of ergotamine have been previously reported. Severe anginal pain occurred in a 49 year-old woman with an exophthalmic goiter after each of the 3 intramuscular injections of 0.5 mg. of ergotamine tartrate. Amyl nitrite did

TABLE 1. THE EFFECT OF ERGOTAMINE PREPARATIONS ON ORGANICALLY INVERTED T WAVES

Name	Age	Diagnosis	Medication	15 minutes		30 minutes		45 minutes		Reactions
J.Y.	45	Rheumatic heart	Gynergen	I to U	O	I to U	O	I to U	O	none
C.I.	59	Left vent. hypertrophy	Gynergen	I to U	I to U	I to U	I to U	I to U	I to U	none
F.S.	55	Rheumatic heart	DHE 45	O	I to -I	O	I to U	O	I to U	nausea vomiting
J.P.	75	Coronary thrombosis	DHE 45	I to U	I to U	I to U	I to U	I to U	I to U	angina for 10 hours
G.R.	75	Left vent. hypertrophy	DHE 45	I to +I	I to +I	I to +I	I to +I	I to +I	I to +I	angina for 2 hours
J.K.	56	Left vent. hypertrophy	Gynergen	O	I to U	O	I to U	O	I to U	none
E.M.	58	Leutic heart	DHE 45	O	U to -U	O	U to -U	I to +I	U to -U	angina, died
J.C.	65	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	angina
A.F.	65	Left vent. hypertrophy	DHE 45	O	O	O	O	O	O	nausea vomiting
G.D.	60	Left vent. hypertrophy	DHE 45	O	O	O	O	O	O	none
A.A.	44	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	none
A.K.	48	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	nausea
A.S.	60	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	none
J.C.	63	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	angina
S.L.	35	Rheumatic heart	Gynergen	O	O	O	O	O	O	tingling in legs
R.S.	45	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	none
C.R.	59	Left vent. hypertrophy	Gynergen	O	O	O	O	O	O	none
C.S.	46	Old coronary thrombosis	Gynergen	O	O	O	O	O	O	none
S.G.	39	Rheumatic heart	Gynergen	O	O	O	O	O	O	nausea vomiting

LEGEND:

I to U = inverted to upright  
 O = no change  
 U to +U = increase in the uprighting  
 U to -U = decrease in the uprighting  
 I to -I = inverted to less inversion  
 I to +I = inverted to greater inversion

show any change in the electrocardiogram and the patient who died during a severe anginal attack developed the electrocardiographic change after 45 minutes, long after the pain had appeared. One patient had a normalization of the electrocardiogram in spite of severe anginal pain (Fig. 3). This same lack of parallelism exists in spontaneous attacks of exertional angina and in attacks induced by the exercise test.

not bring relief and morphine had to be given.<sup>5</sup> The same author observed a death a few hours after the administration of ergotamine in a 60 year-old woman with hyperthyroidism.<sup>6</sup> Similar to our own case with the same unfortunate outcome was another observation.<sup>20</sup> A 43 year-old woman with an aortic regurgitation and angina on effort, developed a severe attack of angina pectoris after the administra-

tion of 1 mg. of ergotamine tartrate. Nitroglycerine did not relieve. The pain gradually increased in intensity and the patient died 24 hours after the injection. During this period there was a depression of the RS-T segments in Leads I and II similar to that observed during her spontaneous attacks of angina pectoris. The post mortem examination revealed a syphilitic aortitis, insufficiency of the aortic valves and a marked stenosis of the coronary ostia.

Lichtman reported 3 patients with anginal pain after the oral administration of ergotamine tartrate.<sup>8</sup> One was a 65 year-old man with advanced generalized arteriosclerosis who developed tachycardia, precordial distress and a fall of blood pressure after the oral dose of 1 mg. of ergotamine. Carter reported a woman with migraine who developed immediate palpitation, tachycardia and substernal pain after the intramuscular injection of 0.5 mg. of ergotamine tartrate.<sup>2</sup> Three hours later auricular fibrillation occurred which reverted to normal sinus rhythm at 5 hours but the substernal pain persisted for 9 hours. Repeated electrocardiograms were normal.

In view of our experiences and the reports in the literature, the employment of ergotamine and its derivatives as has been recently suggested in patients with coronary disease is hazardous and should be avoided. Coronary artery disease is a contraindication for these drugs.<sup>16</sup>

We are not able to explain the long duration of the untoward effects of ergotamine nor can we conclude whether only those patients with coronary artery disease will show these toxic reactions, or whether these effects may occur in patients with normal coronary vessels. Our investigations were terminated because of the death of the last patient to whom we administered ergotamine.

**Conclusions.** Ergotamine preparations cannot be used to differentiate the functionally inverted T waves from those which are inverted because of organic heart disease; temporary normalization of the inverted T waves may occur in both conditions after administration of ergotamine.

The use of ergotamine preparations in patients with coronary artery disease, is hazardous.

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# THE USE OF QUINIDINE SULPHATE IN THE TREATMENT OF HICCUP, A PRELIMINARY REPORT

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THIS report is based on our experience in the use of quinidine sulphate in the treatment of 9 cases of persistent hiccup, in 6 of which the drug proved effective (Cases 1, 3, 5, 6, 8, 9). In 2 patients (Cases 2, 4) the hiccup was improved but did not stop altogether, and in 1 (Case 7) this treatment was apparently of no help.

Hiccup has been described as an intermittent clonic contraction of the diaphragm often associated with clonic contraction of the accessory muscles of respiration, or as a sudden clonic spasm of the diaphragm accompanied by a spasmodic closure of the glottis. It is due to a great variety of causes which irritate either the afferent pathway to the centers in the upper cervical part of the spinal cord, the centers themselves or their efferent pathways to the muscles. Reflexes through the vagus may play a part in its production. Kremer<sup>12</sup> (1922) was of the opinion that the clonic contraction of the diaphragm is set off by an irritation of the respiratory center. This can be initiated by: (a) disturbance in the central nervous system; (b) a chemical irritation resulting from anoxemia, uremia, and toxic products; and (c) by stimulation of the sensory fibers of the phrenic and sympathetic nerves and also by reflexes through the peripheral nerves.

A multitude of conditions may incite the attacks, such as a diseased state in the abdomen, chest or brain, and systemic infections as well as psychologic factors. Among the frequent conditions which pre-

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cipitate these seizures are disorders of the esophagus and stomach, such as gastritis and gastric dilatation, intestinal obstruction, ileus, strangulated hernia, acute appendicitis, acute pancreatitis, peritonitis, renal disease with azotemia, liver disease, tumors and inflammatory disease of the mediastinum, disease of the heart and pericardium, brain tumor, meningoencephalitis, epidemic encephalitis, cerebrovascular accident, typhoid fever, and other severe infections.

The methods of treatment are numerous. Among the procedures commonly mentioned are: pressure upon the phrenic nerve between the heads of the sternocleidomastoid muscle, drinking cold water, holding the breath, or the induction of sudden fright. Gastric lavage will often give relief when irritation of the gastric mucous membrane is present. Apomorphine, gr.  $\frac{1}{8}$  hypodermically, or hyoscine hydrobromide, gr.  $\frac{1}{200}$ , may be given and repeated after 3 hours. Morphine by itself rarely succeeds in stopping an attack. Benzyl benzoate ( $\frac{1}{2}$  dram of a 20% solution) sometimes stops the attacks. Inhalations of amyl nitrite and chloroform have been used. Application of an ice bag to the neck, ethyl chloride sprayed on the epigastrium, repeated traction of the tongue, pressure on the eyeballs, mechanical dilatation of the esophagus, and pressure upon the ribs near the origin of the diaphragm, have all been tried. Inhalation of 5 to 10% carbon dioxide in oxygen may be pursued until the patient has had an

absence of hiccup for a 1 minute period. If hiccup recurs, as it often does, inhalation of carbon dioxide should be begun again. In intractable cases, Weeks<sup>18</sup> (1931) suggested that the patient should be *examined fluoroscopically to determine the side of the diaphragm involved*. The phrenic nerve on the affected side is then exposed and anesthetized; crushing or avulsion may be required to stop the attack. Occasionally bilateral phrenicotomy has been performed (Campbell<sup>4</sup>, 1940). The pros and cons of this method should be carefully considered before it is used. This procedure results in decreased pulmonary ventilation on the affected side and may further embarrass an already impaired cardiovascular system.

Following the failure of the usual methods to stop an attack of hiccup in a patient who was becoming rapidly exhausted (Case 1), for reasons mentioned later, the use of quinidine was suggested by one of us. In view of the recent experience that more beneficial effects were obtained by the use of large doses in the treatment of ventricular tachycardia, a similar regimen was pursued in this patient. As far as we know this procedure has not been used previously in the treatment of hiccup.

Short histories of our 9 cases follow:

**Case Reports.** CASE 1. A. B., a white man, 75 years of age, poorly nourished, was admitted to the hospital on June 23, 1947. He had suffered 3 previous attacks of myocardial infarction, but had had no recent cardiac episodes. Hiccup had been present for 10 days and was refractory to the usual treatment at home. His general condition was poor. Moderate dyspnea was present. The heart sounds were of poor quality and the normal cardiac rhythm was interrupted by frequent extrasystoles. He had been taking digitalis for several years and was adequately digitalized. An electrocardiograph showed evidence of myocardial damage and digitalis effects. Treatment in the hospital for the hiccup with oxygen, carbon dioxide, alcohol intravenously, ether rectally, and the usual sedatives and antispasmodics was unsuccessful in relieving the hiccup. The patient was rapidly becoming weaker. On the 4th hospital day (after 14 days of hic-

cuping) 10 grains of quinidine sulphate were administered by mouth and within one-half hour the hiccup ceased, but recurred in 2 hours. Two successive doses of 10 grains of quinidine sulphate given 1 hour apart relieved the hiccup for 8 hours. Ten grains of quinidine sulphate again relieved the hiccup for 12 hours. The same dose of quinidine was repeated and the hiccup did not recur.

A total of 50 grains of quinidine sulphate was administered in a period of 2 days. Response to each dose was noted within about 2 hours. The extrasystoles were completely eliminated and a slight increase in the intraventricular conduction time was noted. The patient was discharged on the 11th hospital day, markedly improved.

CASE 2. L. B., a colored man, 67 years of age, was admitted to the medical wards with a diagnosis of prerenal azotemia secondary to diarrhea and hematemesis. The blood urea nitrogen was 137 mg. per 100 cc. and the carbon dioxide combining power was 27 volumes per cent. Roentgen ray of the chest revealed evidence of bilateral caseous tuberculosis. He had had hiccup continually for 72 hours. Following the administration of 9 grains of quinidine sulphate intramuscularly, the hiccup ceased 30 minutes after the injection but recurred in 2 hours. A small dose of quinidine was again administered. The hiccup stopped 15 minutes but recurred in 2 hours. He was given 5 grains of quinidine by mouth every 3 hours for 3 doses. The hiccup stopped 1 hour after the 1st dose. On the following day, quinidine sulphate, grains 9 intramuscularly, was again given for an attack of hiccup. It stopped in about 10 minutes and he was relieved for 2 hours. A similar dose was again given and the hiccup promptly disappeared. He was then placed on a maintenance dose of quinidine, 6 grains every 3 hours, orally, for the next 18 hours. During the latter part of each 3 hour period the hiccup recurred. In the next 3 days he had several short attacks of hiccup which were not considered to be of sufficient length to require therapy. The patient died 3 days later with azotemia and terminal bronchopneumonia.

**COMMENT.** The results of quinidine administered for hiccup in this case seem to indicate that 9 grains given intramuscularly were effective in stopping the hiccup. However, this effect was only temporary



and lasted about 2 hours. The oral administration of 6 grains every 3 hours as a maintenance dose was only partially effective in controlling the hiccup.

CASE 3. W. B., a negro 60 years of age, was admitted to the hospital with a diagnosis of adenocarcinoma of the prostate. He was found to have uremia secondary to a bilateral pyelonephritis. The blood urea nitrogen was 150 mg. per 100 cc. He had been hiccuping continually for 4 days and had received no relief from the usual measures.

On July 27, 1947, at 11 A.M., 9 grains of quinidine sulphate were given intramuscularly. At 1:10 P.M., it was noted that the frequency of hiccup had been reduced in rate. He was then given quinidine sulphate, 9 grains, orally; this was repeated in 2 hours. At 5:30 P.M., the hiccup ceased but recurred at 10 P.M.

On July 28, 1947, at 11:30 A.M., the patient was given 9 grains of quinidine intramuscularly and at 1:30 P.M. his hiccup was relieved. He had no recurrence of singultus after this time. This patient died in azotemia 1 week later but had no recurrence of the hiccup.

CASE 4. W. B., a negro 52 years of age, was admitted to the hospital with a diagnosis of intestinal obstruction. Operation revealed many adhesions between the transverse colon and anterior parietal peritoneum. Postoperatively he developed atelectasis with bronchopneumonia. Following the operation, hiccup developed and continued intermittently for 3 days. Ethyl chloride sprayed upon the abdomen and chest and the inhalation of amyl nitrite failed to relieve the hiccup. On July 28, 1947, the 3d postoperative day, he received 9 grains of quinidine intramuscularly at 5:35 P.M., and 9 grains intramuscularly at 6:35 P.M. The singultus stopped 10 minutes following the 2d dose. Similar doses of quinidine were given at 7:35 P.M. and 9:30 P.M. The hiccup remained quiescent until 12 P.M., at which time he received another intramuscular injection of the same amount of quinidine. The hiccup was again arrested within 15 minutes from the time of administration and remained so for 22 hours. At 3 A.M., another attack stopped about 10 minutes after the injection. No evidence of hiccuping was encountered after this time until the following afternoon. Because the patient was vomiting and since none of the intramuscular preparation was available, he

was given 10 grains of quinidine dissolved in 20 cc. of normal saline solution by the intravenous route. Following the injection the hiccup decreased in frequency from 35 to 18 per minute, and a diminution in depth was noted. The hiccup did not stop immediately but was gone about 2 hours later. These attacks did not recur during the remainder of his stay in the hospital (6 days).

The patient was discharged to the surgical clinic.

CASE 5. V. R., a negro, 46 years of age, was admitted to the genito-urinary department with a diagnosis of urinary extravasation, secondary to a gonorrheal urethral stricture. The blood urea nitrogen was 29 mg. per 100 cc., and the carbon dioxide combining power was 37 volumes per cent. The patient had experienced hiccup intermittently for 48 hours and continuously for 12 hours previous to treatment. Quinidine sulphate, 9 grains, was administered intramuscularly at 2 P.M., and every hour thereafter for 3 hours. The hiccup gradually decreased in frequency and stopped 4 hours after the last dose was given. He had received no other medication for the treatment of hiccup.

The patient experienced short mild episodes of hiccuping the following day, which ceased without medication. He had no recurrence of singultus for the next week of his hospital stay. He was then discharged to the genito-urinary clinic.

CASE 6. A. B., a negro, 35 years of age, was admitted to the orthopedic ward with a diagnosis of Pott's disease and tuberculosis of the mediastinum. On admission the temperature was 103° F., pulse 120, and respirations were 30 per minute. The patient had experienced hiccup continually for 5 days previous to treatment and was becoming rapidly exhausted. At noon, quinidine sulphate, administered orally in dosages of 10 grains every hour for 3 doses, was vomited. No inhibition of the singultus occurred. At 6:30 P.M., 9 grains of quinidine were administered intramuscularly. The hiccup stopped 2 hours after the 1st dose was given. Two similar doses at intervals of 1 hour were administered and the patient remained free from hiccup until 9 o'clock the next morning at which time the singultus recurred. The hiccup again ceased in 1 hour after the intramuscular administration of 10 grains of quinidine sulphate, and the patient remained

free of singultus for 24 hours. On the 3d day the hiccup recurred. Three successive doses of quinidine, 9 grains intramuscularly, were given. The hiccup stopped after a short time and did not recur for 24 hours. On the 5th night another attack of hiccup ceased after the administration of 9 grains of quinidine intramuscularly. The patient remained free from hiccup, except for 2 short episodes which were not treated, until the 8th day. At this time, the singultus recurred and since the hiccup became continuous and exhausting, he was given quinidine, 9 grains intramuscularly, for 2 weeks at intervals of 1 hour. The hiccup ceased a short time after the 1st injection. On the 9th day hiccup was again encountered. He received 9 grains of quinidine intramuscularly, at 1:30 P.M. and the singultus ceased at 1:45 P.M. He received another 9 grains of quinidine intramuscularly, at 2:30 P.M. On the 10th day the singultus recurred twice. Following the intramuscular administration of 9 grains of quinidine, the hiccup ceased.

The patient is still in the hospital receiving treatment for his original tuberculous condition, and has not had an episode of hiccup during the remainder of the period of observation (10 days).

COMMENT. In this patient, who had been hiccuping continually for 5 days, quinidine was of definite value in stopping the hiccup. Repeated administration of the drug resulted in cessation of the attack, as a result of which the patient remained free of hiccup for 12 to 24 hours at a time.

CASE 7. D. C., a negro, 62 years of age, was followed in the medical clinic with a diagnosis of singultus apparently of psychogenic origin. He presented a history of episodes of hiccup intermittently for 3 years. Examination showed no abnormalities except a blood pressure at 165/116, and probable slight enlargement of the left ventricle. Treatment was begun at a time when the patient had been hiccuping for 14 hours continuously. Quinidine sulphate, 9 grains, was administered intramuscularly at 10:15 A.M. This was followed by 10 grains orally at 11:15 A.M. A decrease in hiccup was noticed at 1:15 P.M. Ten grains of quinidine were again administered at 1:45 P.M. In about 2 hours the patient's hiccup stopped for a period of 1 hour and 15 minutes. He was

then given a maintenance dose of quinidine, 5 grains every 3 hours, throughout the night. Upon returning to the hospital 18 hours later, the patient stated that he had taken the medication as prescribed with no relief from the singultus. He was given 9 grains of quinidine intramuscularly and the hiccup stopped 12 hours later. He had taken a short nap, and it was during this time that the hiccups were relieved. The hiccup recurred 22 hours later. The patient has not returned to the clinic for further study.

COMMENT. It is very difficult to evaluate the results obtained in this patient because he was not under observation during the time in which he was taking the maintenance doses of quinidine. It will be noted that in this case small doses were used and we are not certain that he followed the routine of the prescribed medication.

CASE 8. J. J., a negro, 57 years of age, was admitted to the hospital on October 13, 1947, with a provisional diagnosis of vomiting due to intermittent pyloric obstruction. His blood analyses on admission were typical of a severe alkalosis. The blood sugar was 116 mg. per 100 cc. blood urea nitrogen 78, total blood chloride 337 mg., carbon dioxide combining power 104 volumes per cent. He gave a history which was very incomplete. The following points are significant: He had experienced some epigastric distress for which he had taken fairly large amounts of sodium bicarbonate. He had had no bowel movements for an undetermined period previous to admission. He had been hiccuping continually for 52 hours previous to the institution of treatment and was becoming rapidly exhausted. On October 15, 1947, he was given quinidine sulphate intramuscularly in a dosage of 9 grains every hour for 3 doses. His hiccup stopped 40 minutes after the 1st injection. The relief from hiccup was followed by a rapid improvement in the patient's condition. The patient has had no recurrence of his hiccup for the 8 days he was observed. During this period the abnormal chemical findings returned to normal.

CASE 9. J. S., a negro, 66 years of age, was admitted to the hospital on October 14, 1947, with a diagnosis of hypertensive cardiovascular disease and a recent cerebrovascular accident. He had singultus constantly for 36 hours previous to medication. Quinidine sul-

phate was given intramuscularly in the dosage of 10 grains every hour for 3 injections. The hiccup was noted to have slowed in frequency 30 minutes after the first injection and stopped completely 2 hours after the initial medication, but recurred later that night. Because of the restlessness and extreme illness of the patient, it was considered inadvisable to give more quinidine. He was given 72 grains of sodium amytal intravenously. His hiccup continued, and the next morning he was again given 10 grains of quinidine sulphate intramuscularly every hour for 3 doses. His hiccup ceased 1 hour after the initial injection and remained absent for 62 hours. No further treatment with quinidine was given this patient. The patient died 2 days later following another cerebrovascular episode.

**Discussion.** Although not discussed in detail in the case reports, (except for Case 1), the usual well-known methods of treatment of hiccup were tried in most of these patients with little or no success. Our experiences in the above group of patients suggest that quinidine has an apparently beneficial effect in controlling attacks of hiccup. The possible theoretical basis for its action is discussed below. In our patients the drug was given by mouth, intramuscularly, and in 1 patient intravenously. While it is felt that administration by mouth is effectual, its action is apparently more dependable when given by the parenteral route. By the intramuscular route the absorption is certain, uniform, and relatively safe. It is felt that a more effective response will be obtained by the use of high doses given over a relatively short period of time rather than small doses given over a prolonged period. Such a procedure has recently been shown to be a more satisfactory one in the treatment of many cases of ventricular tachycardia. Delevett and Poindexter<sup>5</sup> have shown that when a single dose of 15 grains of this drug is given by mouth the concentration reaches its maximum in a period of from 2 to 4 hours, and that it required a certain level in the blood, namely about 1 mg. per

liter,<sup>5</sup> to stop an attack of nodal tachycardia. † It is quite likely that a similar situation may exist in respect to hiccup. That this drug may not work equally well in all cases will depend upon the underlying cause of the increased irritability and its degree. We are as yet not certain as to the dose of the drug and frequency of administration which may be necessary to stop a paroxysm. At present it is suggested that an initial dose of 10 grains, preferably given by the intramuscular route, be repeated hourly for 3 to 4 doses. If the paroxysm stops, the patient may be put on a maintenance dose of 5 grains orally every 2 to 3 hours. If the paroxysm recurs, the initial high doses should be repeated. The use of cinchona derivatives in man by mouth and by vein has already been extensive enough to demonstrate their relative safety.

The use of quinidine is not recommended in all patients. It is suggested for those cases of persistent hiccup where the usual procedures are ineffective and where the continuance of the paroxysms results in exhaustion of the patient.

**PROBABLE MECHANISM OF ACTION.** That the cinchona alkaloids have a pronounced effect on striated muscle was recognized by Santesson<sup>15</sup> (1892), Secher<sup>16</sup> (1915), Fürth and Schwartz<sup>6</sup> (1909), and Harvey<sup>9</sup> (1939). Brody and Sollman<sup>7</sup> (1923) showed that quinidine lengthens the refractory period of skeletal muscle. The results obtained by these authors in experiments with quinidine on striated muscle were quite parallel to the clinical results with quinidine in auricular fibrillation, as conceived by Lewis and others. These authors state that "In both cases the prolongation of the refractory period makes the muscle independent of a rapid rate of stimulation that ordinarily produces more or less complete tetanus and enables it to adopt the slower rhythm and more extensive excursions that are so much more efficient for working a pumping mechanism." Harvey<sup>9</sup> (1939) showed that quinine

decreases the ability of the muscle to respond to and hold a tetanus. This is due to an effect directly on the muscle which increases the refractory period. The excitability of the motor end plate is lowered, so that the response to nerve stimulation is reduced. This is best seen in a partially curarized muscle. When quinine is injected under these conditions, the curarization becomes complete. This action is also in part responsible for the abolition by quinine of the quick response of the muscle to injected acetylcholine. That quinine may have a direct effect on nerve tissue is suggested by Stravaky<sup>17</sup> who found quinine acts directly as a paralyzing drug on the secretory fibers of the auriculo-temporal nerves.

The normal potentiation of the twitches caused by physostigmine due to repetitive response to a single nerve volley, is prevented by the previous administration of quinine or is counteracted promptly when the drug is injected during a period of potentiation.<sup>12</sup> Weiss found that the fibrillary twitchings produced in the cat by prostigmine were abolished by the intravenous injection of quinine. The repetitive response to a single stimulus which occurs after veratrine is also removed by quinine. This occurs in both the normal muscle and the muscle of which the motor nerve has previously been cut and allowed to degenerate. Harvey<sup>9</sup> (1940) has shown that the curareform action of quinine is greatly increased by the introduction of the quaternary ammonium ion in the quinoline ring as observed by the action of quinine methochloride. The main features of the action of quinine methochloride on the mammalian nerve muscle preparation resembles curarine, blocking neuromuscular transmission and leaving the response of the muscle to direct stimulation unimpaired. Like curarine, it causes a depression of the response of the motor end plate and the ganglion cell to nerve impulses and to acetylcholine, but does not interfere with the normal liberation of acetylcholine from the preganglionic nerve endings. This

drug has been used successfully in the prevention of fractures in the course of convulsive therapy with metrazol.<sup>1</sup> Wolf<sup>20</sup> (1936) showed the value of quinine in the treatment of myotonia congenita. The chief clinical manifestation in this condition is a contraction in skeletal muscle after the end of a voluntary stimulation. This state is symptomatically relieved by quinine but is made worse by prostigmine. Quinine increases the muscular weakness of patients with myasthenia gravis, thus manifesting an opposite effect to that of prostigmine in these 2 conditions.<sup>8,9,11</sup> The cinchona drugs have also proven of value in the treatment of night cramps of the lower extremities.<sup>7,13</sup> This condition appears to be due to a lasting tetanic contraction of a muscle group due to reflex bombardment of the myoneural junction by a stream of impulses from some neighboring source of irritation. The effectiveness of quinine here is due in part to its action directly on muscle tissue, but more important is its effect in interrupting the reflex arc by blocking myoneural pulse transmission. To quote Gootnick,<sup>7</sup> "Quinine acts in relieving night cramps much as does digitalis in depressing the bundle of His in auricular fibrillation by cutting down the number of impulses that can get through to stimulate the muscle to contraction."

If attacks of hiccup are the result of spasmodic contractions of the diaphragm and other muscles of respiration, the impulses for which are transmitted through nerve tissue, it is our feeling that quinidine could stop a paroxysm of hiccup in 2 ways: (1) by a direct effect of the drug on the diaphragm as well as on the muscles of respiration; and (2) by blocking the nerve impulses at the myoneural junction. There is some suggestive evidence that this drug may have a direct effect on nerve tissue which may block impulses through the vagus and other nerves.

**Summary.** 1. Experience with the use of quinidine in the treatment of 9 cases of hiccup is discussed. Quinidine was appar-

ently effectual in stopping the paroxysms in 6 cases, was partially successful in 2 and failed in 1 case.

2. In patients with intractable hiccup the use of this drug may be efficacious in stopping the seizures when other methods have failed.

3. The probable mechanism of the action of quinidine in the treatment of hiccup is discussed.

Addendum: Since this paper was submitted for publication, our experience with subsequent cases of hiccup has been somewhat similar to that reported above. One point of interest might be added: in those patients where hiccup followed abdominal operations and subsequent fluid loss by vomiting or other means, electrolyte imbalance, notably hypocalcemia and hypopotassemia, was apparently a factor which tended to induce or help maintain the attack of hiccup. In addition to the administration of quinidine, the correction of this electrolyte imbalance was an important factor in stopping the hiccup attacks.

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# SULFATE AND PHOSPHATE EXCRETION IN URINE OF PATIENTS ON RICE DIET\*

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THE course of renal and hypertensive vascular diseases has been modified by the use of a diet consisting of rice, fruit, and sugar.<sup>5,6,7,8</sup> Ninety-five per cent of the caloric intake is furnished by carbohydrate; in 2000 calories there are about 20 gm. of protein and not more than 5 gm. of fat, 0.2 gm. of chloride, and 0.15 gm. of sodium. On this regime the nitrogen equilibrium is maintained, and the patient can be made to gain weight if the caloric intake is raised.

with hypertensive vascular disease without evidence of renal failure. The diet of many of the patients had been restricted before the rice diet was started. The daily urinary excretion of total sulfate and of inorganic sulfate was determined in 14 patients (10 men and 4 women) who had followed the rice diet for periods of 30 to 46 days (average 36 days). The urinary inorganic phosphate was measured in 17 patients (13 men and 4 women) who had followed the diet for 14 to 59 days (average 34 days).

The results are summarized in Table 1.

The inorganic sulfate excretion in all

TABLE 1.—EFFECT OF RICE DIET ON SULFATE AND INORGANIC PHOSPHATE EXCRETION IN URINE OF PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE

	Before	Range		Before	Average	
		Rice Diet	After		Rice Diet	After
Total Sulfate (mg S in 24 hrs.)	761–471		254–58	592		126
Inorganic Sulfate (mg S in 24 hrs.)	547–362		165–40	452		81
Ethereal Sulfate (mg S in 24 hrs.)	328–52		115–15	140		45
Inorganic Phosphate (mg P in 24 hrs.)	1055–501		435–170	761		289

Quantitative data on all aspects of metabolism are needed to determine the factors responsible for the favorable effect of the rice diet on the course of hypertensive and renal diseases. This paper summarizes the changes in urinary phosphate and sulfate excretion which occur on the rice diet.

**Procedure.** The sulfate and phosphate were measured in each of 3 successive 24 hour urine collections. The sulfates were determined by the benzidine method of Rosenheimer and Drummond as modified by Hoffman and Osgood.<sup>4</sup> The inorganic phosphate P was determined with a photo-electric colorimeter according to the phosphomolybdate method of Fiske and SubbaRow.<sup>2</sup>

The studies were carried out on patients

14 patients showed a decrease ranging from 68 to 92% (average 82%). The ethereal sulfate excretion increased in 2 patients and fell in 12. For the 14 patients the average decrease was 56%. The total sulfate excretion in all 14 patients showed a decrease ranging from 58 to 91% (average 79%). The ratios of inorganic sulfate to total sulfate ranged from 0.56 to 0.90, average, 0.77, before the diet, and from 0.41 to 0.81, average 0.65, after the diet.

The inorganic phosphate excretion in all 17 patients fell from 40 to 75%, with an average fall of 62%.

In Table 2, the lowest amounts of

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sulfate and phosphate in a single 24 hour urine collection in this group of patients are recorded and compared with the amounts excreted on an egg-milk diet, a starch-cream diet and in fasting.

**Discussion.** The data are of value for two reasons. First, they demonstrate that the kidney is called upon to excrete much less phosphate and sulfate when a patient is on the rice diet than when he is on a regular diet or while fasting. What this means in terms of renal work is not known. Observations are needed on patients with hypertensive disease on a rice diet with added phosphate and sulfate. Secondly, these data serve as a rough check

on the data previously reported on nitrogen equilibrium.<sup>6</sup> The patients had a daily protein intake of 20-25 gm. But they could not have been breaking down appreciable amounts of body protein because of the low excretion of nitrogen, phosphates, and sulfates as compared to that of fasting individuals.

**Summary.** The average amount of inorganic sulfate excreted in the urine of 14 patients on the rice diet was about 90% lower than that of persons on a normal diet; the average amount of ethereal sulfate was about 45% lower, that of total sulfate was about 85% lower. The average amount of inorganic phosphate was about 70% lower than that of persons on a normal diet.

TABLE 2.—MAXIMAL-MINIMAL URINARY SULFATE AND PHOSPHATE EXCRETION ON EGG-MILK DIET, STARCH-CREAM DIET, FAST AND RICE DIET

	Egg-Milk Diet* (120 gm. of protein)	Starch-Cream Diet* (6 gm. of protein)	Fasting§ (10th day)	Rice Diet (20-25 gm. of protein) Lowest Values
	Highest Values	Lowest Values		
Total Sulfate (mg S in 24 hrs.)	1315†	194†	579†	50
Inorganic Sulfate (mg S in 24 hrs.)	1252	168		25
Ethereal Sulfate (mg S in 24 hrs.)	76	24		2
Inorganic Phosphate (mg P in 24 hrs.)	1613†	276†	709†	117

\* According to Folin<sup>3</sup>

§ According to Benedict<sup>1</sup>

† Calculated as 90% of Total Sulfur.

‡ Calculated as 90% of Total Phosphorus

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# BRUCELLOSIS AND MULTIPLE SCLEROSIS

## CUTANEOUS REACTIONS TO BRUCELLA ANTIGENS

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BECAUSE of the multiplicity of its manifestation, brucellosis has often been compared to syphilis. Innumerable case reports attest the ability of acute brucellosis to produce focal disease of all sorts. In the central nervous system it may cause meningitis, encephalitis, and encephalomyelitis. It is also well known that chronic Brucella infection produces lesions in the eye.

We have reviewed 560 cases of chronic brucellosis to determine the frequency of neurologic symptoms. *Definite sensory and motor changes* or disturbances of the 2nd, 6th, or 8th nerves were found in 28 patients; in 2 additional patients the fully developed picture of multiple sclerosis was present. This suggests the possibility that multiple sclerosis might be a central nervous system manifestation of chronic brucellosis.

In order to investigate this hypothesis 118 consecutive cases of multiple sclerosis have been studied. The diagnosis was made in each case by a member of the neurosurgical or neuropsychiatric departments of the Cleveland Clinic.

**Methods.** Three methods of Brucella skin testing were employed. An unaltered, heat-killed, suspension of suis and abortus strains of Brucella combined (6 billion per cc.) was used as the standard test on all patients throughout the study. Each intradermal injection consisted of 0.04 cc. Brucellergen (0.1 cc.) and Brucella antiserum (0.04 cc.) the latter according to

the technique of Foshay<sup>4</sup> were used as confirmatory tests in about half the cases of multiple sclerosis.

Skin tests were used on 2 control groups. Group 1 consisted of 56 rural residents of middle ages having a variety of clinical disorders. Group 2 was comprised of patients with neurologic conditions other than multiple sclerosis or encephalomyelitis.

Definite standards of interpretation were established. The standard vaccine type or bacterin test was read according to Harris,<sup>5</sup> description of this method. The evolution of this reaction commonly requires 48 to 72 hours to reach its maximum, but nonspecific reactions of erythema without induration may be seen in the first 24-hour period. In those in whom the response is feeble, the persistence of induration and discoloration for a week or more supports the positive interpretation of the reaction. Hence, a positive reaction is recorded when there is a visible and palpable infiltration of the dermis accompanied by a surrounding erythema.

Brucellergen produces a more delicate and rapid reaction than the bacterin method. A positive reaction is recorded when there is edema and erythema between 24 and 48 hours. A positive antiserum reaction consists of a central wheal with a surrounding flare averaging 4 to 5 cm. in diameter appearing within 10 minutes of the injection. The interpretation of antiserum reactions is facilitated by the use of a control injection of non-immune or specially filtered serum.

**Results.** The results of the 3 types  
(659)



of cutaneous tests in the multiple sclerosis group are given in Table 1.

TABLE 1. RESULTS OF DIAGNOSTIC TESTS FOR BRUCELLOSIS IN 118 CASES OF MULTIPLE SCLEROSIS

Test	Total cases	Negative	Positive	Percent positive
Killed Brucella organisms.....	118	3	115	97
Brucellergen.....	55	2	53	96
Polyvalent anti-brucella serum...	55	0	55	100
Antibortus serum.....	55	0	55	100
Filtered serum.....	44	38	6	14

The results of the bacterin test in the control groups are given in Table 2.

TABLE 2. RESULTS OF BACTERIN TESTS FOR BRUCELLOSIS IN 98 CONTROL CASES

	Total cases	Negative	Positive	Percent positive
Group 1.....	56	44	12	21
Group 2.....	42	29	13	31

Three patients with multiple sclerosis are listed as having negative bacterin tests. In 1 of these patients it was not possible to observe the reaction at the proper time nor to secure a satisfactory description. It was therefore recorded as negative. This patient did have a positive reaction to each antiserum test. The other 2 patients with negative bacterin reactions were not tested with Brucellergen or antiserum tests. The 2 patients who had negative Brucellergen tests had definite positive reactions to bacterin and to antisera as well. Of the positive reactions to bacterin 10 were classed as weakly positive. In these erythema was less than 2 cm. in diameter, but in all cases induration and discoloration were present for at least a week. Seventy-nine of the positive bacterin reactions were graded as moderately positive with

erythema of 2 to 4 cm. in diameter, and 26 cases exhibited more extensive erythema and were termed strongly positive. Actual tissue necrosis occurred in 6 of these. Approximately the same proportion of weak, moderate, and strongly positive reactions were seen among the patients in the control groups.

To be certain that the positive reactions observed in multiple sclerosis were not the result of an abnormal degree of cutaneous reactivity, the latest patients in the series were also tested with 0.1 cc. each of old tuberculin (1:10,000), histoplasmin (1:1000), and coccidioidin (1:1000). The results of these tests are given in Table 3.

TABLE 3. RESULTS OF TUBERCULIN, HISTOPLASMIN AND COCCIDIOIDIN TESTS IN 10 CASES OF MULTIPLE SCLEROSIS

	Patients	Positive	Negative
Old Tuberculin.....	41	15	26
Histoplasmin.....	34	5	29
Coccidioidin.....	34	0	34

A foreign body effect on the part of the whole organism appears not to be involved. This factor was investigated by skin testing 10 patients with a vaccine of *H. influenzae* and 19 with a vaccine prepared from a streptococcus isolated from sour cream. Neither of these preparations produced any persisting induration or erythema.

The possibility that the skin reactions were due to other types of infection is more difficult to evaluate. Cross agglutination reactions definitely occur between brucellosis, tularemia, cholera, Flexner type dysentery, and *B. proteus* infections. However, there was nothing to suggest the presence of any of these infections, other than brucellosis, in any of the patients studied.

The cutaneous antiserum reaction of Foshay,<sup>4</sup> even more than Brucellergen, speaks for the specificity of the Brucella

reactions. Foshay has shown that the antiserum reaction was specific for 19 different strains of streptococci. He found that the test involved a reaction between an antibody to the specific polysaccharide of an organism and the polysaccharide itself which is deposited in the tissues of the infected person. This antibody could be removed by filtration through Fuller's earth without lowering the titer of agglutinins. The control serum used in this study was prepared in this manner. Foshay has cautioned against the possibility of false positive reactions from commercial preparations because they may contain antibodies to polysaccharides of incidental organisms. Twenty-five *Brucella* negative individuals have been tested with the polyvalent antiserum and 3 reacted positively.

Forty *Brucella* positive patients who did not have multiple sclerosis were tested with the polyvalent antiserum and were found positive in all instances, although in 2 the reaction was delayed 24 hours. It is felt that the high frequency of positive reactions to *Brucella* antiserum in cases of multiple sclerosis is further evidence of the possible existence of brucellosis in these individuals. The fact that all cases tested reacted to antiabortus serum as well as the polyvalent antiserum may be of some significance. Foshay reported a limited experience with the several types of *Brucella* antiserum but indicated that the cutaneous reactions were specific for *melitensis*, *suis*, or *abortus* strains. The writers have encountered only 1 *Brucella* positive patient who reacted to polyvalent antiserum but failed to react to antiabortus serum.

Agglutination reactions were done in 23 cases of multiple sclerosis. The reaction was negative in 18 and positive in 5 in titers of 1:20, 1:20, 1:40, 1:160, and 1:320, respectively. The last 2 titers must be discounted because they

were taken 4 to 5 weeks following the skin test. Although one would expect to find low titers in chronic infections and negative reactions in those in whom the infection is in an inactive stage, these figures are still far from impressive. Eisele, McCullough and Beal<sup>2</sup> have pointed out some of the vagaries of the agglutination reaction.

As a further check on the agglutinations Eisele generously consented to test specimens of our patients' sera in the University of Chicago laboratory. The results in his laboratory and those in the Cleveland Clinic are given in Table 4.

TABLE 4. COMPARISON OF AGGLUTINATION TEST RESULTS IN 2 LABORATORIES

Patient	Cleveland	Chicago (Dr. Eisele)
1	negative	1-80
2	1-20	1-80
3	negative	negative
4	1-360	1-1280 and partial 1-2560
5	negative	1-40
6	1-160	1-320
7	negative	1-40
8	negative	negative
9	negative	1-20
10	negative	negative
11	negative	negative
12	negative	negative

All of these patients had positive skin tests and all but patients 2 and 11 had multiple sclerosis. The differences are striking and, like the laboratory discrepancies noted by Eisele *et al.*, are probably due to differences in sensitivity and selectivity of the antigens. Cases 4 and 6 were those taken several weeks after the skin test. The extremely high titer in case 4 could not be wholly the result of the previous skin test, but that in case 6 might be. Consequently, if the latter case be excluded, the agglutination test was positive in 5 out of 9 cases of multiple sclerosis. All multiple sclerosis patients with positive reactions had evidence of active disease; those in whom the ag-

glutinations were negative showed few if any new neurologic signs.

**Discussion.** The peculiar geographic distribution of multiple sclerosis is one of its most distinctive features. In the United States the areas of greatest frequency are in the Pacific Northwest and in the Great Lakes basin. These regions are characterized by excessive rainfall, little sunshine, and high milk production. Brucellosis of the abortus type is also prevalent in these areas.

The question naturally arises as to whether the concept of brucellosis as an etiologic agent in multiple sclerosis is compatible with recent fundamental work in the pathogenesis of the latter disorder. An excellent review of this subject has been published recently by Andren.<sup>1</sup> He contends that neither the possibility of local allergy nor the theory of virus etiology necessarily precludes the possibility of vasoconstriction or vascular occlusion as the basic mechanism in multiple sclerosis. The same statement could be applied to brucellosis. Perivascular infiltration, and small vessel thromboses have been noted as basic components of the granulomatous lesions known to be produced by that disease. The plaque-like lesions seen in cases of *Brucella* chorioretinitis are certainly comparable to the plaques of multiple sclerosis and both chorioretinitis and iritis have been seen in a few of the patients of this study.

A case of multiple sclerosis<sup>2</sup> occurring during the course of a remittent *Brucella* infection has been reported in the French literature. Roger *et al.*<sup>3</sup> reported a case of neuromyelitis optica, (essentially an acute and rapidly fatal form of multiple sclerosis), with a *Brucella* agglutination titer of 1:500 in the spinal fluid. A similar case without fatal termination was reported by Mc-

Cullagh and Clodfelter.<sup>6</sup> Roger<sup>7</sup> has also recorded 10 cases of brucellosis in which there were transient sensory and motor disturbances which he believed to be the result of cerebral vasospasm occurring during both the early and late course of the disease. A mild cyto-albuminous reaction in the spinal fluid was found in 9 of the cases and a positive culture was obtained in one.

The investigations of Teague<sup>9</sup> have been cited as evidence against the infectious origin of multiple sclerosis. He reported failure to isolate spirochetes from the blood and spinal fluid of cases of multiple sclerosis as had been previously reported. He also recorded that some of the rabbits inoculated with blood or spinal fluid died of wasting infections with an unidentified small, gram negative bacillus in the blood stream. We have inoculated both rabbits and guinea pigs with blood and spinal fluid from 5 cases of multiple sclerosis all exhibiting signs of recent activity. The only definite result to date is the acquisition of a deep regard for the difficulties encountered in this sort of investigation. A number of animals have died of a granulomatous disease, but cultures have been either sterile or contaminated.

**Summary.** 1. A high degree of cutaneous reactivity to *Brucella* antigens has been found in a group of patients with multiple sclerosis.

2. The known pathologic features and geographic distribution of multiple sclerosis and brucellosis are not incompatible with some relationship. The possibility of a connection between these two diseases warrants further investigation.

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# ERRATUM

In the article on an Epidemic of Tularemia, Figs. 4 and 5 on pages 421 and 422 of the October issue, should be reversed; *i.e.*, the illustration marked Fig. 4 should appear above Fig. 5 on next page, and vice versa.

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# PROGRESS OF MEDICAL SCIENCE

## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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PROFESSOR OF OBSTETRICS AND GYNECOLOGY AT THE HOSPITAL OF THE  
UNIVERSITY OF PENNSYLVANIA

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### ENDOMETRIOSIS

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THE pathological entity classified under the name of endometriosis has attracted widespread attention since it was first described<sup>o</sup>. It is a condition in which endometrium is situated in a position in the body other than in its normal confines in the uterine cavity. Two general pathological types exist. The first, known as adenomyosis, or internal endometriosis, exists in the muscular wall of the uterus itself, and the second, known generally as external endometriosis, consists of the seeding and development of endometrial implants in locations outside of the uterine wall itself. The latter type may be present in any one of a great variety of positions. These endometrial implants respond physiologically to cyclic hormonal stimuli from the gonads, and have been demonstrated to have the same structural changes as normally situated endometrium at the various phases of the ovarian cycle.

**Etiology.** The true cause of endometriosis is still unknown, but many

theories have been advanced in an effort to explain the occurrence of this pathological condition. Only a few have withstood the tests of time and the laboratory. Ranney<sup>66</sup> has classified these theories into two main groups: (1) theories concerning histogenesis, and (2) that concerning possible stimulating influences. Those concerning histogenesis are as follows:

1. *Ectopic endometrium transported from the uterus to the pathological site.* This theory was introduced by Sampson<sup>71</sup> in the early 1920's. It was based on his own clinical observations and studies in pathology. In essence, Sampson's theory postulated that bits of uterine and tubal epithelium were discharged through the fimbriated ends of the tubes by retrograde flow during menstruation, and that they implanted usually on the ovaries, but occasionally on the pelvic peritoneum, or on the serosa of nearby structures, especially in convenient peritoneal pockets. Sampson had observed that endometriosis

\* See Block's<sup>6</sup> earlier review (1940) in this section.  
(694)

was seldom discovered in women under 30 years of age, and that bilateral tubal patency was present in 97% of the patients he had studied. He noted, too, that endometrial hematomas usually developed on the lateral and inferior surfaces of the ovaries, which are the parts most likely to be contaminated by material regurgitated from the tubes. This theory served to awaken a tremendous interest amongst workers in gynecologic and related fields, and soon the theory was subjected to many clinical and laboratory tests. Endometrial tissue has been artificially transplanted into the liver, spleen, abdominal wall, and anterior chamber of the eye in smaller animals. Typical adenomas of various sizes were formed as a result of this autotransplantation, and these were lined with ciliated columnar epithelium, and contained fluid under pressure. Novak and TeLinde,<sup>59</sup> however, claimed that menstruating endometrium discharged from the uterus is necrotic, and contains chiefly autolyzed constituents, with few, if any, formed elements. It has subsequently been shown that endometrium obtained during menstruation is scarcely viable and hardly able to grow in a manner comparable with intermenstrual endometrial particles.

2. *Mechanical transplantation theory.* There is no doubt that endometrial tissue can be transplanted during surgical procedures. Numerous cases have been reported in which endometriosis has been found in laparotomy scars following pelvic surgery.<sup>7,58,68,83</sup> A case of endometriosis<sup>76</sup> in an episiotomy scar following a normal spontaneous delivery has recently been reported. Numerous writers have reported the transplantation of endometrial tissue to pelvic structures following curettage of the uterus. Endometrial tissue has been successfully transplanted into the pleural and peritoneal cavities in experimental animals. The successful im-

plants usually assume a cystic nature, and respond to the normal ovarian stimulation.

3. *Metastasis theory.* The presence of endometrial tissue beneath the apparently normal peritoneum is not explainable except on the basis of spread through the lymphatic channels draining the uterus. The evidence for lymphatic metastasis is incomplete, and it is likely that further studies on this mode of transmission will be carried on in the laboratory. The other route of metastasis suggested is *via* the blood stream, particularly the venous channels. The evidence in favor of this lies in the reported occurrence of instances of endometriosis in the extremities. The evidence supporting this theory is far from complete, however, and this concept would at best explain only a very small number of cases.

The theory evolving from the concept of ectopic endometrium developed in situ from local cells is as follows:

1. *Celomic metaplasia theory.* The Muellerian duct is derived from the embryonic celomic epithelium and mesenchyme, and forms most of the female genital tract including the endometrium. Other adult derivatives of the embryonic celomic cells may retain the potentiality of forming tissue which is indistinguishable from endometrial tissue. Gruenwald<sup>29</sup> implies simply that the cells which are descendants of the celomic epithelium and which may retain the potentiality of endometrium formation, are present in large numbers in the upper genital organs and pelvic peritoneum. These are present also, to a far lesser extent in the extremities, the upper two-thirds of the vagina, the pleura, the general peritoneal cavity, the umbilicus, and other locations in which endometriosis has been discovered, including the inguinal canal, the serosal surface of the bladder and ureters. The celomic metaplasia theory permits a physiological

explanation, based on embryological and pathological observations, for endometriosis occurring spontaneously in any part of the body, provided, of course, that the basic concept of celomic cell rests can be proven. Conclusive proof of the validity of this theory is at present lacking, and may never be available. As would be expected in a disease whose etiology is so obscure, many other attempts have been made to explain the cause, but none has withstood laboratory experimentation or clinical findings. Perhaps a combination of the theory of Sampson, plus the mechanical transplantation theory and the theory of lymphatic metastasis will serve best to explain the etiology insofar as our present knowledge permits.

**Incidence.** Endometriosis is a disease of women in the childbearing age. Its greatest incidence occurs in the last part of the third decade of life and early part of the fourth decade, but it has been reported as occurring at earlier ages,<sup>20</sup> during the years of waning ovarian stimulation, and in postmenopausal ages.<sup>25</sup> It is probable in many instances that the disease process is initiated at an early age, and is not suspected or discovered until increasing severity of symptoms calls for medical investigation or laparotomy. Fallon<sup>21</sup> and Holmes<sup>26</sup> have both presented evidence suggesting that increasing dysmenorrhea and pelvic pain occurring in the second decade may represent the beginning of endometriosis.

It is impossible to estimate with any accuracy the incidence of endometriosis in the population at large. A great variability is noted in the methods of reporting it. Haydon<sup>20</sup> reports an incidence of 9.84%. Holmes<sup>26</sup> reports an operative incidence of 26%. Sampson has reported endometriosis in 21.6% to 29.5% of his series of gynecologic laparotomies. Meigs<sup>22</sup> reports an incidence of 28% in his private practice as opposed to one of 5.5% in the Massa-

chusetts Hospital group. Hunter, Smith and Reiner<sup>27</sup> report an incidence of adenomyosis of 27.8% in a series of 1556 hysterectomies performed for all causes over a 15 year period. Yin<sup>24</sup> states that endometriosis and adenomyosis are commonly found in Chinese women. Lock and Myers<sup>45</sup> report an incidence of 28% of proven cases in their series. Endometriosis has been recognized more frequently in recent years. It is not certain whether this has been an absolute or relative increase, since many more physicians than ever before are seeking this condition because of its recognized serious implications. Meigs<sup>22</sup> has attributed the increase to several factors. One of these is the modern economic trend favoring delayed marriage, and delayed and infrequent childbearing. Meigs is of the opinion that menstruation is not supposed to occur monthly for years without interruption, resulting in many menstrual cycles without union of the sperm and ovum. Stimulation by the varied hormonal reactions of menstruation of the celomic cells might cause them to grow and produce Muellerian growth. This view is supported by his statistics showing an incidence of 28% in his private practice as opposed to one of 5.8% at the Massachusetts General Hospital. He advocates early marriage, and early and frequent childbearing to offset the increasing incidence.

**Pathology.** The pathological features of endometriosis consist of aberrant masses of endometrial tissue in a variety of locations. The ectopic tissue found in these locations has all the macroscopic and microscopic features of endometrium normally situated. There is a tendency to glandular and cystic formations. These respond to the various endocrine influences exerted on the endometrium during the menstrual cycle. Since most of these cysts have no outlet, there is usually pain as-

sociated with the onset of the menses. As these masses of endometrium continue their life cycles, a great deal of fibrosis and scarring occurs in the organs concerned, and dense adhesions develop between the serous coats of the organs. These adhesions are usually deep seated and their separation is very difficult because of the involvement of the seromuscular layers. Mucosal involvement of the bowel does not as a rule occur, but has been reported.<sup>12</sup> When the full thickness of the viscus is invaded, bleeding into the lumen may result. Thickening of the bowel wall and proliferation of the smooth muscle may encroach on the lumen of the bowel, and produce a partial or complete obstruction. It is frequently very difficult to differentiate grossly this type of endometriosis of the bowel from carcinoma.

The organs most frequently involved in this disease process are, in the order of frequency, the ovaries, pelvic peritoneum (posterior cul-de-sac with involvement of the uterosacral ligaments), external surface of the uterus, rectovaginal septum, bladder, Fallopian tubes, and sigmoid colon.<sup>30,39,53,65,80</sup> More rarely, the round ligaments, appendix, umbilicus, and other peritoneal organs are involved. In rare instances, endometriosis of the extremities<sup>73</sup> has been reported. Endometriosis of the lungs has been produced experimentally in laboratory animals.<sup>33,34</sup>

The lesions in the ovaries vary in size from that of a pinhead to that of a grapefruit. They vary in color from dusky red to brownish black. The cysts are usually chocolate colored due to discoloration of the thin cyst wall by the contents of the cyst. The thicker walled cysts, however, are somewhat whitish and dull. These cysts characteristically perforate when the intraluminal pressure becomes too great for the cyst wall to withstand, and the organization of the blood which es-

capes from the cyst seals the defect, and bloody fluid again accumulates within the cyst cavity. This organization process results in peri-ovarian adhesions. Other organs in the pelvis are also involved in these adhesions. The pelvic peritoneum may become hyperplastic and present a picture of chronic inflammation. Endometrial implants on the anterior surface of the uterus may produce typical peritoneal adhesions to, and invasion of, the bladder. This may extend through the entire thickness of the wall of the bladder and give rise to hematuria and other urinary symptoms. The characteristic puckering of the peritoneal covering of the bladder is apparent at operation.

More infrequently, endometriosis occurs in regions of the body that are more or less remote from the genital organs. Less than 100 cases of endometriosis of the umbilicus have been reported in the world literature. Endometriosis of the intraperitoneal portion of the round ligament occurs rather frequently, but only a few cases of the disease have been reported as occurring in the inguinal portion of the round ligament. When this occurs, it may be quite difficult to differentiate it from hernia.<sup>16,24</sup> Endometriosis of laparotomy scars are noted by many authors. The majority of these occur following operations on the uterus or Fallopian tubes. Wood, Diebert and Kain<sup>81</sup> reported a case of endometriosis which was located in the ileum, 3 inches from the ileocecal junction. The lesion in this case was hard, and consisted of a constricting band of fibrous tissue. Schlicke<sup>73</sup> has reported a case of endometriosis in a 35 year old Filipino which occurred on the posterior aspect of the left thigh. Clinical endometriosis of the lungs has not yet been reported, but Hobbs and Bortnick<sup>33</sup> think that many cases may be mistakenly diagnosed as tuberculosis, cancer or benign lung tumors, and they are of the



opinion that, if sought, many cases of endometriosis might be discovered. Primary endometriosis of the cervix uteri is very rare.<sup>35</sup> To date, there have been only a few cases of perineal endometriosis following episiotomy, and only one in a spontaneous delivery.<sup>74</sup> Endometriosis is not frequently found in association with malignancy of the generative organs.

**Symptoms.** It is generally agreed that the most constant symptom of this disease is dysmenorrhea. This is of the acquired type, and usually progressive. Counseller<sup>14</sup> states that vesical and, or, rectal pain superimposed on an acquired dysmenorrhea is almost always diagnostic. Diffuse pelvic soreness, brought about or aggravated by walking or jarring of the pelvis in any way is also suggestive. Dyspareunia is frequently a presenting symptom. Most of the patients are found to be infertile, despite the fact that patent tubes are found in a large percentage of cases. When endometriosis is found to be the cause or an associated factor in a sterility problem, the solution is frequently very difficult, for a cure of the endometriosis too often requires a radical procedure on the reproductive organs. Even in those cases in which conservative measures are carried out, the results as far as fertility is concerned are not often satisfactory.

Jeffcoate<sup>38</sup> has demonstrated that in about 10% of his patients with endometriosis, pyrexia was a significant factor in making the diagnosis. The degree of fever was not high, 101 to 102° F. being the highest recorded, and its occurrence variable, as it is sometimes intermittent throughout the cycle. The hyperpyrexia typically occurs *during* menstruation, and gradually disappears 1 to 2 days after the flow has ceased. Body temperature normally rises premenstrually, and falls with the onset of flow, so that an elevation *during* each period should be regarded

with suspicion. Other chains of symptoms may develop with involvement of other organs. The ureters may be constricted and produce symptoms of the associated hydronephrosis or ureteral colic. Intestinal obstruction may develop. Localized bluish swelling of isolated lesions in the extremities or in postoperative scars may develop during the menstrual periods. Bimanual examination of the pelvis is very important in making the diagnosis. One may find a cystic ovarian mass, which is usually very tender. Beading of the uterosacral ligaments is characteristic when present. Generalized tenderness throughout the pelvis may be found, and may necessitate an examination under anesthesia.

A careful case history, taken with a high index of suspicion, is necessary for diagnosis of this disease. A careful log of the menstrual periods of the patient, with special reference to the presence of increasing dysmenorrhea, infertility, and dyspareunia, and pelvic pain on urination and defecation is essential for the diagnosis.

**Complications.** It is important to recognize that symptoms may arise in organ systems other than the genital tract. The most frequently involved extragenital systems are the urinary and the gastro-intestinal tracts. Glenn and Thornton<sup>26</sup> reported 2 cases of obstructing endometriosis of the ileum in 1940. They were able to find only 4 similar cases in the literature. Wood, Diebert and Kain<sup>51</sup> reported a hard fibrous constricting band only 3 inches from the ileocecal junction which proved to be an endometrioma on microscopic examination. This is the only case of a similar nature reported since Glenn and Thornton's report. Sutler<sup>79</sup> states that the intestinal tract is a highly significant extragenital location for endometriosis. He found involvement of the intestinal tract in 35 patients; the appendix in 25, the ileum

in 1, and the rectosigmoid in 9. Thierstein and Allen<sup>80</sup> differentiate between a deep and superficial type of endometriosis of the bowel, and state that the former is more likely to be the cause of intestinal obstruction. The radiologic picture of intestinal obstruction due to endometriosis is somewhat characteristic. Jenkinson and Brown<sup>39</sup> have reported relatively long filling defects of 4 to 7 inches demonstrable by barium enema, which are sharply demarcated as in carcinoma. Fixation and exquisite tenderness on palpation are found during fluoroscopic examination. The mucous membrane, however, is essentially intact. In carcinoma of the bowel, the mucosa is usually involved, and the constant filling defect is not so tender to palpation. McGuff, Dockerty, Waugh and Randall<sup>61</sup> reported 16 cases of intestinal obstruction due to endometriosis, which represent the total seen at the Mayo Clinic. They stressed the presence of the usual symptoms of endometriosis, plus the presence of a long history of intestinal symptoms which suggest progressive intestinal obstruction with frequent exacerbations at the menses as the most important points in establishing the clinical diagnosis of this disease. Diarrhea and vomiting, frequently found in intestinal obstruction from other causes, are encountered, but the presence of gross blood in the stools is almost never encountered. When it is found at the time of the menstrual period, it is of significance. Sigmoidoscopic examination almost always reveals the presence of an intact mucous membrane. Patton and Patton<sup>62</sup> have emphasized the absence of lymph node changes, which is helpful in making the gross diagnosis at the operating table.

Endometriosis of the *urinary bladder* may occur in any woman of menstrual age. In a series of 46 patients with endometriosis of the bladder collected

by Moore, Herring and McCannel,<sup>56 42</sup> had had either previous pelvic operations, or, at the time of examination had some disease of the reproductive system. Kahle, Vickery and Maltry<sup>41</sup> had previously noted this fact, and the report by O'Connor and Greenhill<sup>61</sup> adds confirmation. Dreyfuss<sup>18</sup> presented a case of so-called "internal endometriosis" of the bladder, in which the endometrial cells were thought to originate from bladder epithelium. No serosal or other implants were found at operation. This is the only report encountered in the literature that makes mention of this type. O'Connor found in 7 of the 58 patients whom he studied that the endometriosis was supposedly confined to the bladder with no other intra-abdominal lesion present. Leventhal and Solomon<sup>44</sup> reported a case of slow constriction of the ureters by an endometrioma of the pelvic peritoneum and rectovaginal septum. In this case, the ureters were displaced medially, and a bilateral hydronephrosis was demonstrated. Urinary complaints are usually cyclic, and consist of bladder fullness, dysuria, frequency and urgency. The severity of these symptoms vary, the intensity being dependent upon the proximity of the lesion to the trigone, and upon the size of the endometrioma. Hematuria occurs only if the mucosa of the bladder is invaded. It was reported in only 13 of Moore's 46 cases, and in less than one-third of O'Connor's series. The lesion is palpable in the base of the bladder in about half of the cases. If the mucosa is involved, the lesion is easily identified by cystoscopic examination. A bluish-black tumor is seen, usually on the bladder floor, either between or just above the ureteral orifices. The tumor has a cystic surface, bleeds easily, and is surrounded by a bullous edema. If doubt exists, a biopsy taken through the cystoscope will establish the diagnosis in the majority of cases. An endo-

metrial cyst of the left kidney in a 40 year old patient was reported by Marshall.<sup>48</sup> This patient had complained of swelling and pain in the left flank for 16 months. No relation between the menstrual cycle and the severity of the symptoms was established in the history. No evidence of pelvic disease was present, and there was no involvement of the peritoneum, Gerota's fascia, or renal capsule.

**Treatment.** No rule of thumb exists for the treatment of endometriosis. Each case must be individualized, and, perhaps, in this disease as in no other, the judgment of the physician plays a very important role. Many factors enter the picture, and influence the choice of method to be employed; the age of the patient, the extent of the lesions, the involvement of important structures and the ease of mobilization at operation, the desire of the patient for children, and the severity of the symptoms.

It is now well established that endometriosis is under the direct control of the hormonal cycle governing the menstrual cycle, and that the elimination of the ovarian hormones will cause a regression and atrophy of the endometriomas almost anywhere that they exist. It is a form of treatment that is almost always effective, but it is attended by the accompanying disadvantageous symptoms of the artificial menopause in younger women, and the cessation of the reproductive function in patients who might want to bear children. Castration, whether surgical or radiological, is a radical procedure to perform on younger patients afflicted with this disease. It is a procedure which can always be done in the event that there is progression of the disease or continuation of severe symptoms following more conservative attempts at arrest of the disease.

It is probable that many cases of endometriosis are never discovered.

This indicates that many mild forms exist, and that in these no specific treatment is necessary. It is thought by many that incidental cases 'discovered at laparotomy' should be treated. Doubtlessly, many early seedlings can be excised before fibrosis and scarring with deep invasion of adjacent organs have developed. Of course, no one can say that simple excision will prevent the development of other lesions, but this procedure is relatively simple with the abdomen already opened, and can be performed with little or no additional risk. Obvious chocolate cysts of the ovaries should be removed, but, with care, it is often possible to preserve normal portions of the ovaries. This is only of value if there exists no other evidence of endometriosis involving other structures, for as long as there remains any functioning ovarian tissue the lesions in the other organs may be activated. In this regard, it might be well to mention that hormonal therapy with any of the estrogens following castration for endometriosis is liable to be followed by reactivation of the disease. Counsellor<sup>60</sup> has reported on the use of ovarian autografting for endometriosis, and claims good results in 4 of 5 cases in which the procedure was used. In his cases, however, all the diseased tissues were resected, and the grafts were used primarily to prevent or to control menopausal symptoms.

Endometriosis of the urinary tract frequently poses a difficult problem in treatment. It is generally conceded<sup>25, 29, 46, 56</sup> that transurethral fulguration has no place in the treatment of endometriosis of the urinary bladder. Of course, if the ureters are involved, the risk of excision is great. In all those cases in which a reasonable chance of resection of the endometrioma exists, whether by simple excision or by segmental resection of the bladder, the local procedure should be performed, especially if the patient has expressed

a desire for children. In those cases in which the hazards of resection tend to increase the operative mortality, a radical operation on the generative organs is the procedure of choice.

Jenkinson and Brown<sup>39</sup> have taken the stand of Cattell, whom they quote as having stated in 1937 that it was almost always necessary to remove both ovaries in a patient who presented deep lesions of the rectum and sigmoid. Mayo and Miller<sup>49</sup> and others<sup>62,76</sup> are also of this opinion. Some authors<sup>80</sup> believe that radiation castration is of value, but only if biopsy has confirmed the diagnosis. The treatment of intestinal obstruction caused by endometriosis is always surgical. A preoperative diagnosis will oftentimes save the patient a resection of the bowel, and treatment will consist of bilateral oophorectomy and hysterectomy, with or without a temporary complementary colostomy if deemed necessary because of the degree of obstruction present. The therapy of ileal lesions will consist of internal decompression with the Miller-Abbott tube or similar device, restoration of fluid and electrolyte balance, followed by resection of the involved loop of ileum, and primary anastomosis. The performance of panhysterectomy and oophorectomy depends on the presence and degree of associated pelvic disease. If, however, the patient is desirous of a future pregnancy, and there is a reasonable chance thereof, and evidence exists indicative of fair ovarian function, a conservative operation on the ovaries might be performed, with resection of the involved bowel. McGuff, Dockerty, Waugh and Randall<sup>51</sup> claim that the prognosis of patients who have had obstruction of the bowel due to endometriosis is excellent. The chief factor in deciding whether to perform radical or conservative surgery on the ovaries is the desire for and possibility of future pregnancies. The possibilities for future successful pregnancies are

not very good as a rule in the course of this disease. Low<sup>46</sup> was able to salvage only 9 children out of 249 cases, 90 of which were treated conservatively. Meigs<sup>52,53</sup> claims a pregnancy salvage rate of between 9 and 29%. Payne<sup>64</sup> salvaged pregnancy in 9% of his series; Lock and Myers<sup>45</sup> in 30%. The prognosis for increased fertility following therapeutic measures for endometriosis must certainly be guarded. Androgen therapy has been tried in the past several years with good success, especially when dealing with recurrences following the menopause or castration.<sup>15,32</sup> Miller<sup>54</sup> has used testosterone preoperatively to diminish the activity of the process so as to allow for radical surgery, and achieved excellent results without any masculinizing effects.

**Summary.** Endometriosis is a disease of women in the child-bearing age. It is of unknown etiology, although many theories have been advanced to explain its onset and pathogenesis. It is a disease very frequently associated with infertility and underdevelopment of the genital tract. Its manifestations are very protean, and it has been shown that almost every organ system of the abdomen may be the site of aberrant endometrium. Endometriomas have been found in the groin, and extremities, and may be experimentally transferred to the lungs, anterior chamber, and other organs of the body. The diagnosis is frequently easily made when a careful history reveals an acquired dysmenorrhea, pelvic pain, especially on jarring, and exacerbations at the time of the menses. Examination reveals characteristic shotty masses in the rectovaginal septum most easily palpated by rectum.

The treatment of this disease demands a high degree of judgment on the part of the surgeon. In single lesions involving only the serous coat of a given structure, it is frequently pos-

sible simply to resect the lesion. It is safer to err on the side of radicalism in treatment, however, than to attempt preservation of ovarian function when there is some involvement of both adnexae or when there is involvement of one adnexa and adjacent uterine wall. One exception to this, of course, is the case where the patient is very desirous of a future pregnancy. Conservative measures cannot be recommended for the relief of sterility, although they should be performed wherever possible in the hope that fertility might be restored. The reported salvage rate of subsequent pregnancies ranges from 9 to 30%. Patients on whom conservative measures are performed should be ad-

vised that future operative treatment might be necessary.

Endocrine therapy with the androgens has a very definite place in the treatment of this disease, but should be reserved for those cases which have recurrences of symptoms following castration, and in those few cases where a recurrence of symptoms develops after the menopause. Estrogens should not be used for control of menopausal symptoms for fear of stimulating any remaining lesions.<sup>8,23,40</sup>

The use of Roentgen-ray therapy in endometriosis has not been met with enthusiasm, for it is thought that a definite diagnosis must be made by biopsy before irradiation therapy is instituted.

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# PEDIATRICS

UNDER THE CHARGE OF

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## THE LIVER DISEASES OF INFANCY AND CHILDHOOD

A Brief Summary of Reports and Papers, 1934-1948

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VIRAL hepatitis, which became a major problem during World War II, is now being detected much more frequently in civilian populations over the world. The thought is growing that many patients with obscure liver disorders, infants and children as well as adults, have been ill with unrecognized viral hepatitis. With this concept in mind, and in order to clarify the types of liver disease which are actually encountered in the pediatric age period, a survey has been made of the papers on liver disease in infancy and childhood reported as such in the medical literature of the past 15 years.

Since in most cases the pathogenic agent is not known, the descriptions and classifications in the reports have been based almost solely on morphologic grounds. Apparently similar lesions have often been described under different names by different authors. Due to the difficulties involved in interpreting conditions of obscure origin, particularly when studied by others, little attempt is made in this review to alter the diagnoses as originally made by the reporting authors.

**Tumors. Cysts.** Solitary cysts of the liver have proved clinically important

only when large enough to mechanically produce disturbing symptoms or to be physically detectable. White,<sup>72</sup> in 1936, described a huge cyst, apparently of bile duct origin, in a 4 month old male infant. In his discussion, White mentioned that less than 6 such non-parasitic cysts have been reported in the first decade of life. The majority of cysts are congenital in origin, and are classified as follows: (1) dermoids, (2) cysts lined with ciliated epithelium from primitive foregut, (3) lymphatic cysts, (4) bile duct cysts, (5) cysts of blood-vessel and endothelial origin. Atakam<sup>5</sup> described a congenital hepatic cyst in a 9 year old girl which was diagnosed as an ovarian cystoma and was surgically removed. Montgomery<sup>16</sup> described several clinically recognized cysts which he thought were probably of biliary origin. He stated that 25 out of 108 cases reported to date were in children under 13 years of age.

In this connection, mention should be made of congenital polycystic disease of the liver. In this disease, multiple cysts are scattered through the liver and usually through other organs as well.<sup>4,67</sup> The pancreas, kidneys.

spleen, ovary and lungs may also be affected. A discussion of the condition is given by Waterson and Morgan.<sup>68</sup> Ewing<sup>19</sup> states that the association of polycystic disease of the liver and kidneys may be found at autopsy in congenitally malformed infants, especially females.

*Adenoma.* Wilens<sup>73</sup> described a benign solitary hepatic adenoma in an 8 month old white male infant. Rupture of a dilated overlying vein necessitated surgery. At operation, the tumor was inoperable.

*Cavernous Hemangioma (Hemangio-Endothelioma).* These vascular tumors produce progressive abdominal swelling due to an enlarging liver. Gastrointestinal symptoms and anemia are frequent, whereas jaundice and ascites are infrequent.<sup>30</sup> One case report describes a 3 day old newborn infant who died of rupture of a cavernous liver hemangioma following difficult labor.<sup>37</sup>

*Neuroblastoma.* Two cases of hepatic neuroblastoma have been reported, the patients being infants.<sup>23,56</sup> In both, the histologic pattern was that of "sympathoma". A fibroblastoma of the liver has been described by Zuckerman.<sup>80</sup>

*Primary Carcinoma.* The usual presenting syndrome in the many reports is that of a progressive enlargement of the liver, either symmetrical or asymmetrical. Steiner<sup>62</sup> reviewed 105 reported cases in 1938, and felt that 75 presented enough positive evidence to justify the diagnosis. To these he added 2 personally observed cases: one, a 4 month old girl, the other, a 16 month old boy. Of the 77 patients, 41, or slightly more than half, were under 2 years of age at the onset. There were 51 boys and 24 girls, with the sex not recorded for 2 patients. Steiner thought that the frequent occurrence of the tumor at birth or in early infancy suggested that a congenital factor was important in its causation, at least in some cases. The symptoms were not

characteristic, being dependent to a large extent upon the mechanical effects of the growth in the liver. Pain was a common symptom. There were frequent disturbances of nutrition, with anorexia, anemia, and loss of weight, although some children appeared well nourished. Jaundice and ascites occurred infrequently. The onset of symptoms was sometimes sudden, but more often insidious, with gradual slow enlargement of the abdomen. The average duration of life following the appearance of symptoms was 4 months. None of the patients survived. Steiner's classification of the cases according to the type of lesion is as follows:

Type of growth	Number of cases
Hepatoma	
Primary carcinoma (liver cell).....	30
Adenocarcinoma (liver cell) .....	15
Carcinoma hepatocellulare solidum ....	2
Medullary carcinoma .....	5
	52
Cholangioma	
Primary carcinoma .....	3
Unclassified	
Primary carcinoma .....	22

Metastasis outside the liver occurred in 27.2% of the patients. Extension was sometimes into the portal and hepatic veins, and sometimes into the inferior vena cava. Metastasis to the lymph nodes occurred in 9 patients, to the lungs in 16, and to the pleura, pericardium, spleen and pancreas in 1 each. The tumor may spread within the liver by direct invasion of the capillaries, and at autopsy may be found widely disseminated.

*Teratoma.* Two instances of malignant hepatomas having teratoid features were reported.<sup>50,70b</sup> Sarcomatous, osteoid and cavernous areas were noted in these tumors. One patient with multiple tumors of the *hamartoma type* was also reported.<sup>60</sup>

*Trauma and Rupture.* In the newborn period, rupture of the liver is usually



ascribed to trauma, although infarction and hypoprothrombinemia have been deemed contributory factors in at least 1 case. Henderson's<sup>50</sup> review describes 47 cases of hepatic hemorrhage encountered in 1,312 postmortem examinations of stillborn and newborn infants, and summarizes the general manifestations of the lesion. The surface of the liver adjacent to the anterior abdominal wall was the site of the hemorrhage in most of the children. The incidence was higher in large infants and in prematures. Obstetrical abnormalities or difficult deliveries were concomitants in the majority of cases.

The sudden appearance of anemia in the first few days of life should make one consider rupture of a subcapsular hematoma.<sup>55</sup> The diagnosis of intraperitoneal hemorrhage can often be confirmed by paracentesis.

Extravasations beneath the capsule of the liver are fairly common in the newborn period. Most of the hemorrhages probably resorb without being clinically recognized. Only when the hematoma ruptures into the abdominal cavity are symptoms produced. Most cases are recognized after the development of this complication, or as incidental findings at autopsy or operation.

Subcapsular hemorrhage with rupture occurs also in older children, usually secondary to trauma, although a tumor or infarct may be the predisposing cause.<sup>6,12</sup> Bluish bronzing of the skin about the umbilicus may direct attention to the presence of blood within the peritoneal cavity.<sup>6</sup>

**Abscess. Bacterial.** Pyogenic abscesses of the liver have been reported by a number of authors. They may be secondary to umbilical infection of the newborn<sup>10</sup> or to an appendiceal abscess.<sup>74</sup> Those associated with septicemia are often multiple. Slesinger and Antiles<sup>53</sup> give an etiologic classification of pyogenic abscesses, derived from Kutsumai,<sup>10</sup> as follows:

Dysentery	43	Tuberculosis	11
Trauma	19	Umbilical infections	7
Mesenteric infections	17	Typhoid fever	6
Intestinal parasites	17	Influenza	2
Appendicitis	16	Unclassified	7

In this connection, mention may be made of Brim's<sup>9</sup> findings of postmortem liver cultures on 100 stillborn and dead newborn infants. *E. coli* was isolated from the liver in 3 and an anaerobic streptococcus, a species of genus *Bacteroides*, and a gamma streptococcus in each of 3 others.

**Amebic.** Amebic abscesses, though rare, can occur in childhood.<sup>64,65</sup> The clinical manifestations differ little from those seen in adults, and the response to surgical drainage and anti-amebic medications is good.

**Others.** Liver abscesses due to *ascaris lumbricoides*,<sup>50</sup> *echinococcus*,<sup>20</sup> and *trichomonas hominis*<sup>51</sup> have been reported, as have multiple tuberculomata,<sup>70c</sup> and gummas and cirrhotic lesions in congenital syphilis.<sup>41</sup> Several instances of obscure granulomas in the liver have also been recorded.<sup>14,26</sup>

**Infiltrations. Xanthomatoses.** The liver, with its large number of reticulo-endothelial cells, exhibits prominent infiltrations in the xanthomatoses. Several articles have stressed the liver infiltration. Weidman and Stokes<sup>72</sup> described a 4 year old white girl with extensive xanthoma tuberosum due to infectious cirrhosis. Wood<sup>76</sup> reported an unusual instance of primary liver carcinoma in an 8 month old white girl who, at autopsy, had lesions suggestive of Nieman-Pick's disease. The association of these 2 diseases was attributed to coincidence. Herbert's<sup>72</sup> patient was a 7 year old white girl with arrested growth, enlarged liver and spleen, renal disease with albuminuria and hypertension, and enormous increases in plasma phospholipids and cholesterol. She had repeated attacks of jaundice dating to 2 weeks of age, when a severe

umbilical hemorrhage had occurred.

#### *Intracellular Liver Storage Diseases.*

Glycogen storage disease is the most commonly reported congenital disorder in which the liver cells seem unable to metabolize properly or utilize intermediary metabolic substances, which then accumulate within the cells. Good reviews of glycogen storage disease can be found in the papers by van Creveld,<sup>66</sup> Mason and Andersen,<sup>44</sup> Bridge and Holt,<sup>8</sup> and Manter and Bowman.<sup>43</sup> The variety of clinical and pathological observations has led Mason and Andersen, and also van Creveld, to suspect that the cases probably represent a group of different though related diseases rather than a single entity. Mason and Andersen, after a critical review of 68 cases, have proposed the following classification (condensed slightly from their paper):

Cases in which the main deposit of glycogen was in the liver (glycogen storage disease of the liver).

1. Primary defect probably a complete or a partial inability of the liver to transform glycogen into dextrose and possibly dextrose into glycogen (von Gierke's disease; 34 cases).

- A. Rise in blood sugar after the administration of epinephrine less than 10 mg. per 100 cc. (15 cases).

- B. Rise in blood sugar after epinephrine between 10 and 40 mg. per 100 cc. (11 cases).

- C. No blood sugar curves after epinephrine reported but postmortem observations showed that the liver failed to break down its glycogen (2 cases).

- D. No blood sugar curves after epinephrine and no postmortem enzyme studies reported but postmortem examination revealed a gross excess of glycogen in the liver and the kidney (6 cases).

2. Chronic galactosuria with hepatomegaly, with the liver apparently unable to metabolize galactose normally.

3. Fructosuria, with the liver apparently unable to form glycogen from levulose but usually without hepatomegaly.

4. Abnormal regulation of insulin in the body, with glycogen deposited in the liver.

- A. Hyperinsulinism resulting from tumor

of the islands of Langerhans with large amounts of dextrose given.

- B. Diabetes mellitus with large amounts of insulin and dextrose given.

5. Unclassifiable in the preceding groups, sometimes because of inadequate data.

The characteristics common to most, if not all, cases of glycogen storage disease seem to be: (1) marked hepatomegaly, (2) fasting hypoglycemia with resulting ketosis, (3) little or no rise in blood sugar level following an injection of epinephrine, (4) high glycogen content in the liver, and (5) abnormal stability of liver glycogen after death. Secondary effects of impaired glycogenolysis are: (1) hypoglycemia which may induce ketosis, cerebral symptoms and possibly impair resistance to infections, (2) excessive conversion of carbohydrate to fat, which sometimes leads to obesity, and (3) negative nitrogen balance resulting from increased formation of sugar from protein and leading to impaired growth. Other evidences of liver disturbance include a defect in prothrombin formation, disturbance in methylation and, in infancy at least, lipemia. That the disorder may be familial is indicated by the report of Abramson and Kurtz<sup>1</sup> describing 4 fatal cases among siblings of one family.

Debré and associates<sup>13</sup> have emphasized that some children have chronic fatty enlargement of the liver in association with both disturbances of carbohydrate metabolism and hyperlipemia, and Kramer, Grayzel and Solomon<sup>38</sup> and others have described similar cases. These children may exhibit all the phenomena of glycogen storage disease along with the associated fat disturbance. Chemical examination of their livers reveals an unusually high fat content. Some have had a high glycogen content in addition, whereas others have had no such increase. Xanthomatous lesions may be present in the skin and elsewhere. A critical analysis

of the reported cases has been made by van Creveld.<sup>66</sup>

**Hepatomegaly of Unknown Etiology.** There are many reports in the literature of hepatomegaly of obscure origin occurring in children. McFarlane and Branday<sup>49</sup> describe 18 instances of painless abdominal enlargement due to an enlarged liver with ascites, seen in colored children in Jamaica. This is a chronic illness appearing in the age group 1 to 10 years, with intermittent fever, anorexia, jaundice and vomiting. Nutritional deficiency appears to be a contributing factor. Sometimes the spleen is enlarged as well, leading to a disturbance resembling Banti's syndrome. Several authors believe the pancreas may be responsible in some way for the hepatic enlargement.

**Inflammation and necrosis due to poisoning.** The liver is one of the chief detoxifying organs in the body. Most textbooks of pathology and pediatrics give an exhaustive list of diverse toxins which are known to cause liver inflammation or necrosis, perhaps followed by cirrhosis. Anesthetics, synthetic drugs, toxins of the infectious diseases, and naturally occurring poisons of plant and animal origin have all been implicated or at least suspected of being responsible for liver damage in some patients.

The identity of the noxious agent in any individual patient may not be clearly known, so that occurrence of some poisoning is often made solely on inferential grounds. In these circumstances it is always difficult to rule out viral hepatitis. Newborns as well as older infants and children may be affected.<sup>42</sup> Menten and Andersch<sup>42</sup> have reported 38 instances of liver disease among 299 necropsies of children who had been receiving sulfonamide therapy. Three had toxic necrosis, 9 had toxic central necrosis, and 26 had serious hepatitis and beginning toxic central necrosis. There was no correlation

between the amounts of sulfonamide received and the liver lesions, and the relationship to the sulfonamides was not clear.

Henderson<sup>31</sup> has described various liver lesions in infants with erythroblastosis fetalis of severe degree. The incidence of cirrhosis of the liver was greater with the increasing length of survival of the affected children.

A number of cases have been reported of liver cirrhosis or necrosis among children due to alcohol,<sup>54</sup> bismuth,<sup>75</sup> mushroom poisoning,<sup>24</sup> copper,<sup>21</sup> and sulpharsphenamine.<sup>17</sup> Price<sup>58</sup> has suggested that barbiturates given to parturient women during labor may exert some toxic influence on the fetal liver.

**Cirrhosis.** Harrell and McBryde<sup>28</sup> classified the etiologic factors of cirrhosis of the liver in humans as follows:

Intoxication of cells by: Metals; organic compounds.

Obstruction to bile by: Congenital defects; tumors, stones.

Obstruction to blood by: Cardiac failure; venous thrombosis.

Infection: Of blood stream, of biliary tract; through effects of toxins.

Parasitism of: Blood; intestinal tract.

Diet and metabolic disturbance by: Alcohol; diabetes, hyperthyroidism.

Combinations of: Intoxication and infection; obstruction and infection.

Unknown causes.

Their report described 20 children with cirrhosis seen at the Duke Hospital, of whom 13 came to autopsy. Their conclusion was that the pathologic picture of cirrhosis in childhood resembled that seen in adult life, but classification is more difficult and often impossible. They suggest that the etiologic factors are often multiple.

**Biliary Cirrhosis.** An orthodox discussion of biliary cirrhosis in childhood is given in the paper by Evans<sup>18</sup> who divided this disturbance into 4 subgroups, as follows: (1) Congenital biliary cirrhosis with or without obliteration of ducts; (2) Infantile biliary

cirrhosis of Indian nurslings; (3) Acquired obstructive biliary cirrhosis—common duct obstruction; (4) Acquired non-obstructive biliary cirrhosis (Hanot's type). Most authors who have described individual cases of biliary cirrhosis, however, report them as such without subclassification. Biliary cirrhosis secondary to congenital aplasia of the extrahepatic bile duct system is much more common than the limited number of reports would indicate.

The diagnostic problems associated with the recognition of congenital defects of the biliary tract have been emphasized by Woolley,<sup>77</sup> who points out that there are no absolute methods for diagnosing these anomalies pre-operatively. Surgical exploration may reveal atresia of part or all of the extrahepatic ductal system, but biopsy specimens are needed for careful study of the liver architecture itself. Woolley comments that of a dozen infants in whom obliteration of extra-hepatic bile passages was strongly suspected, the diagnosis was confirmed at operation in only 3 instances. "The clinical laboratory . . . does not possess a critical test in this condition". The experience of the Reviewers corroborates that of Woolley.

*Familial Cirrhosis.* Cirrhosis of the liver occasionally develops in 2 or more children of the same family.<sup>79</sup> The liver lesions are variously described as hepatomegaly or hepatosplenomegaly, cirrhosis, portal cirrhosis, hepatic sclerosis and so forth. The condition may resemble Banti's disease.<sup>48</sup>

*Atrophic cirrhosis.* Dunsky<sup>16</sup> described a congenital biliary form of cirrhosis in a 2 month old white infant and stated that in infancy the biliary variety is more common than the portal variety. He cites several references to illustrate the frequent association of kidney lesions with this form of cirrhosis, and ascribes the kidney damage to injury from the unusual quantity of

exogenous or endogenous toxins being excreted by it which the damaged liver had not been able to previously neutralize or detoxify. Braid and Ebbs,<sup>7</sup> Webster<sup>70a</sup> and Drummond and Watkins<sup>15</sup> have suggested that Rh incompatibility and lesions resulting therefrom may be responsible for the cirrhosis in some families.

*Infantile Cirrhosis in India.* Cirrhosis and other liver diseases are unusually common in India, and an abundant literature on the subject is accumulating.<sup>11</sup> Prabhu<sup>57</sup> summarizes the findings in 100 cases. The disturbance seems to be more common among Hindus. Its familial incidence is 20 to 30%. It is seen in the wealthy and middle class as well as among the poor. Children aged 1 to 2 years seem the most often affected. There is no sex predilection. Many writers believe that the diet is responsible but no convincing data are available on this point. Prabhu postulates an underlying familial or congenital defect. Infection may be important in the pathogenesis.

The liver disease as seen in India has an insidious onset with progressive liver enlargement, digestive symptoms, and mild hypochromic anemia. The course lasts 1 to 2 years and is usually fatal, but children who survive beyond 2 years often recover. Apparently the prognosis depends upon the extent of destruction of the liver substance during the early acute stages.

*Other Cirrhotic Disturbances.* There are reports suggesting that cirrhosis may be associated with disturbances in calcium and phosphorus metabolism, or with resistance to vitamin D.<sup>22</sup> Gillman and Gillman<sup>25</sup> have described liver damage in infantile pellagra. The liver is often sclerotic in erythroblastic (Mediterranean) anemia.

Amberg<sup>2</sup> divides juvenile cirrhosis into 2 forms. One is a biliary type, which is most common in children between 6 months and 2 years of age.

This is said to last 1 month to 1 year, and carries a high mortality rate. The majority of children under 1 year with cirrhosis have this variety, according to Amberg. In later years, the portal type of cirrhosis predominates. Infantile portal cirrhosis has a progressive course, and few cases have survived more than 5 years, according to this author. Ninety per cent of the children with portal cirrhosis have splenomegaly.

In reviewing the cases reported in the past 15 years, one finds that many authors simply describe cirrhosis of the liver in childhood without attempting an anatomic or etiologic classification. Many of the papers were written before the importance of viral hepatitis was appreciated, and most of the reports do not mention any possible relationship between hepatitis and cirrhosis.

**Acute Yellow Atrophy.** A number of reports of this syndrome have been recorded. The affected children have been of all ages, and the clinical course has usually been abrupt and fatal. Reports of acute yellow atrophy in children occurring in the course of small epidemics of catarrhal or infectious jaundice are of special interest.<sup>33,78</sup> Acute yellow atrophy is clearly not a disease entity, but a fatal syndrome which may complicate any type of severe liver damage.

**Viral Hepatitis.** Both infectious (epidemic) hepatitis and (homologous) serum hepatitis have received an abundance of attention in the past few years. Exhaustive review articles have been prepared by Neefe, Gellis, and Stokes,<sup>77</sup> Stokes,<sup>61</sup> and Havens.<sup>29</sup> Webb and Wolfe *et al.*<sup>60</sup> reported an increased incidence of infectious and homologous serum hepatitis in children during 1944, 1945, and 1946, and stated that non-icteric patients are more frequent than icteric ones. Apley and Wallis<sup>52</sup> concluded from their experience in England that serum hepatitis is rare in

infancy. Parsons<sup>55</sup> reported an example of familial hepatitis in which 4 died of hepatic failure in the second decade of life, 2 are living with hepatic enlargement, 2 are alive and well, and 1 died probably of another cause. The early clinical picture of these cases was highly compatible with infectious hepatitis. Autopsy on 2 of those who died revealed peri-lobular and multi-lobular cirrhosis with areas of cellular regeneration. Dunsky,<sup>16</sup> Moon,<sup>47</sup> and others have described instances of familial cirrhosis among siblings, which may well represent sequellae to infectious hepatitis.

Whole blood, plasma, and blood products have been responsible for transmitting serum hepatitis in children as well as in adults.<sup>10,36</sup> However, no instance of serum hepatitis has been attributed to the administration of gamma globulin. On the other hand, fraction I (the anti-hemophilic fraction) of plasma, prepared according to the method of Cohn and co-workers, has been very recently shown to be capable of carrying the virus of homologous serum hepatitis.<sup>63a</sup>

Neefe and Stokes<sup>53</sup> reported an epidemic of infectious hepatitis which occurred at a summer camp in Pennsylvania. The epidemic was characterized by an unusually high attack rate. From the total camp group of 573, of whom about two-thirds were campers between 3 and 17 years of age, 44% developed hepatitis with jaundice, and an additional 17% had hepatitis without overt jaundice. The clinical picture of hepatitis in these children did not differ from that seen in adults. Epidemiologic observations and transmission experiments provided evidence that the agent responsible for this epidemic was water-borne, and was being excreted in the feces of persons with the disease.

Horstmann, Havens, and Deutsch<sup>21</sup> reported 2 institutional outbreaks of

infectious hepatitis involving children. One institution had 53 cases of hepatitis with jaundice and 56 cases of questionable hepatitis without jaundice. In the 2nd institution, 65% of 68 patients having hepatitis with jaundice were children under 16 years. The distinguishing features of infectious hepatitis as seen in these children were its mildness and short duration. None had

a severe illness with prolonged jaundice or protracted convalescence. It would appear, however, that in childhood the clinical pictures of both infectious and homologous serum hepatitis are not greatly different from what is seen among adults, and the disease may vary in severity from subclinical disturbances at one extreme to rapidly fatal liver atrophy at the other.<sup>27</sup>

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As originally submitted this list contained 251 references; the authors kindly consented to reduce it to its present size in order to conserve valuable space.—Editor.

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# PHYSIOLOGY

PROCEEDINGS OF

## The Physiological Society of Philadelphia

SESSION OF NOVEMBER 16, 1948

**The Oxidation of Ferrocyanochrome-C by Peroxidase and Peroxides.** BRITTON CHANCE,\* Ph.D. (Johnson Research Foundation, Univ. of Penna.).

WHEREAS cytochrome oxidase has generally been recognized as the only physiological oxidant of ferrocyanochrome-c, this paper shows that peroxidases from plants and from milk, in addition to the cytochrome-c peroxidase found in yeast by Altschul, Abrams, and Hogness,<sup>1</sup> can perform this oxidation in the presence of hydrogen peroxide or alkyl hydrogen peroxides.

Contrary to the negative results of Altschul, Abrams, and Hogness,<sup>1</sup> horse radish peroxidase†<sup>1a</sup> is an active catalyst for the oxidation of ferrocyanochrome-c by hydrogen peroxide. In fact, at ferrocyanochrome-c concentrations of about  $1 \times 10^{-6}$  M, this oxidation proceeds as rapidly as would the oxidation of the same concentration of pyrogallol which is usually used to measure peroxidase activity. A similar catalysis is observed when lactoperoxidase†<sup>1a</sup> is used.

The kinetics of the oxidation of ferrocyanochrome-c have been recorded by a sensitive spectrophotometric technique<sup>3</sup> and are found to be unusual; the speed of the reaction is not proportional to the concentration of ferrocyanochrome-c; the reaction velocity does not decrease rapidly until the concentration of ferrocyanochrome-c has fallen to a rather low value. This is interpreted to mean that the rate of breakdown of a complex of peroxidase-peroxide and ferrocyanochrome-c may be a limiting step in the catalysis. For this reason, the turnover number in

this reaction is limited to about one mole of ferrocyanochrome-c per mole of peroxidase per second at 25° C. and pH = 7.0. The corresponding figure for lactoperoxidase is 0.6. The corresponding figure for cytochrome-c peroxidase prepared from yeast was not given by Altschul, *et al.*,<sup>1</sup> but appears to be considerably greater.

Some calculations have been made which show that the turnover number for the oxidation of ferrocyanochrome-c by horse-radish peroxidase is compatible with the observed  $QO_2$  of slices of horse-radish root. The values of 40-100  $\mu$  L/G(wet)/hour for horse-radish root<sup>5</sup> would correspond to a turnover of cytochrome-c of 0.5 to 1.25  $\mu$ M/sec. The peroxidase concentration is 50-175 P.E. per 200 g<sup>2</sup> and corresponds to 2.3 to 7.8  $\mu$ M. The required turnover number for peroxidase is about 0.1 times per second since one peroxidase-peroxide complex oxidizes two ferrocyanochrome-c molecules. This value is well within the *in vitro* value above. The concentration of cytochrome-c in horse-radish root has not yet been measured, but based on Goddard's data<sup>4</sup> for wheat germ, a value on the order of  $10^{-7}$  M may be expected. This is sufficient for peroxidase action.

The source of peroxide for such an oxidation is not known at present; however, several oxidase systems are recognized to reduce oxygen to hydrogen peroxide, xanthine oxidase, diamino oxidase, glucose oxidase,<sup>6</sup> and peroxidase itself in the presence of dihydroxymaleic acid and oxygen.<sup>7</sup>

Although no proof is offered that this mechanism of ferrocyanochrome-c

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† Many thanks are due to Prof. H. Theorell and Dr. K. G. Paul for the loan of pure preparations.



actually occurs under physiological conditions, it is clear that cytochrome oxidase need be no longer taken to be the only catalyst in milk, plants, and yeast which can cause the oxidation of ferrocytochrome-c.

**Physiology of the Breathing Impairment in Anthracosilicosis.** HURLEY L. MOTLEY, Ph.D., M.D., and LEONARD P. LANG, M.D. (Dept. of Medicine Jefferson Medical College and Cardio-Respiratory Laboratory, Barton Memorial Division, Jefferson Hospital).

PHYSIOLOGICAL studies were made on more than 100 anthracite coal miners with respiratory complaints after prolonged exposure to dust. The breathing impairment may be classified in 4 main divisions: (1) decreased ventilation (maximal breathing capacity and vital capacity), (2) increased residual air (degree of emphysema expressed quantitatively as residual air percent of total lung volume), (3) disproportion between alveolar perfusion and ventilation (inadequate alveolar blood flow and reduced oxygen removal from inspired air), and (4) impaired distribution (unequal alveolar aeration) with mean  $pO_2$  gradient between alveoli and arterial blood increased. Multiple involvement may occur contributing to the arterial blood changes (low  $pO_2$ , high  $pCO_2$ , and decreased oxygen saturation) and magnitude of hyperventilation. Except for poor distribution, the main compensatory mechanism is hyperventilation, which is adequate in the early stages and until loss of elasticity of lungs and chest wall structures restricts ventilation to the dyspnea level. The amount of hyperventilation without dyspnea varies widely. Fibrosis in some subjects, without a significant degree of emphysema and reduction in ventilation, results in unequal alveolar aeration and an increased percentage of poorly ventilated alveoli, producing an increased

mean  $pO_2$  gradient from alveoli to arterial blood and decreased arterial  $O_2$  saturation. Studies with high and low levels of oxygenation indicate that the increased  $pO_2$  gradient is primarily one of distribution and not a diffusion difficulty through the pulmonary membrane. Approximately two thirds of the patients had a significant degree of emphysema (residual air 35 to 65% of total lung volume). Vital capacity and maximal breathing capacity were of limited value in appraising the breathing impairment of patients with little or no emphysema but marked distribution impairment. The Roentgen-ray stage of silicosis was poorly correlated with functional change. No single test was satisfactory for correctly evaluating the breathing impairment in the group.

**The Effects of Change of Position Upon the Cerebral Circulation of Man.**<sup>\*</sup> H. A. SHENKIN, M.D., W. G. SCHEUERMAN, M.D., E. B. SPITZ, M.D., and R. A. GROFF, M.D. (Harrison Dept. of Surgical Research, School of Medicine, and Graduate Hospital Univ. of Penna.).

The cerebral blood flow and other cerebral functions were determined by the nitrous oxide method of Kety and Schmidt. A group of 5 normal persons were tilted head up 20 degrees from the horizontal and no change was noted in the cerebral blood flow. The mean carotid pressure dropped from an average of 88 to 73 mm. Hg. in this maneuver, and the cerebrovascular resistance decreased from 1.7 units to 1.4. A group of 6 patients with brain tumor were also tilted head up 20 degrees and here the cerebral blood flow diminished on the average from 51 to 36 cc./100g./min. The mean carotid pressure fell also in this latter group (from 92 to 86 mm. Hg.) but the cerebrovascular resistance increased by 25%.

\* Aided by a grant from the U. S. Public Health Service.

A group of 4 normal patients were tilted head down 20 degrees from the horizontal. In this group the cerebral blood flow actually diminished by 14% although the mean carotid pressure increased 10%. The diminution of cerebral blood flow appeared to be occasioned by a 24% increase in cerebrovascular resistance. Four patients with brain tumor were tilted head down. No significant change in carotid arterial pressure, cerebral blood flow or cerebrovascular resistance were noted. A consistent decrease of cerebral oxygen consumption averaging 17% did occur.

The most plausible explanation for the alterations of cerebrovascular resistance in the normal state and the resultant maintenance of cerebral blood flow at normal levels is the assumption of a nervous control of the cerebral circulation. With this hypoth-

esis the changes of pressure in the carotid vessels could serve as stimuli for reflexes that alter cerebrovascular resistance. In the brain tumor patients such reflexes are depressed and consequently the head up position causes a decrease in cerebral blood flow, and the head down position causes a far less marked reaction in the cerebrovascular resistance than is noted in the normal series.

In the treatment of brain tumor patients, it appears that the head up position is deleterious, insofar as it distinctly reduces the cerebral blood flow. The results of this investigation do not offer any objection to the head down position in the treatment of such patients, if it is desired to aid in the drainage of the upper respiratory tract or prevent aspiration of gastric contents.

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# BOOK REVIEWS AND NOTICES

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EVERYDAY MIRACLE. By GUSTAV ECKSTEIN. Pp. 235. New York: Harper & Brothers, 1948. Price, \$2.75.

THESE essays, conclusive by faint implication only, are in the tradition of M. Henri Fabre. Observation is warmed by the observer's affection for the observed, and the reader shares in the writer's appreciation of individual canaries, chimpanzees, mice, cockroaches and macaws, trusting the accuracy of his briefly focused spotlight. Unlike M. Fabre, Dr. Eckstein has a literary sense of drama, which the great Frenchman escaped. E. T.

MEDICAL CLINICS OF NORTH AMERICA. Nationwide Number. Pp. 253; 33 ill. Phila.: W. B. Saunders, March, 1948. Price, \$16.00 a year.

THIS volume is a symposium on diseases of the digestive system and covers in a concise practical manner most of the morbid states encountered by a gastroenterologist in this country. Bacterial and parasitic diseases are not included, except for amebic hepatitis and an article dealing with the possible relationship of amebiasis to indeterminate ulcerative colitis.

Emphasis is given to the controversial subject of vagotomy by including a clinical conference on this procedure.

The approach to all subjects is from the clinician's point of view with a minimum of discussion of theoretical aspects and of experimental data. This leads to easy reading and also makes this volume a valuable reference when one desires a quick clinical review of a subject. W. S.

THE THEOMATIC APPERCEPTION TEST. By SILVAN S. TOMKINS, Ph.D., Research Associate, College Entrance Examination Board. With the collaboration of ELIZABETH J. TOMKINS, B.A. Pp. 297. New York: Grune & Stratton, 1947. Price, \$5.00.

THE author presents a careful, systematic approach to analysis of projective material obtained by use of the TAT. He stresses ideational content to the exclusion of formal or structural elements which Rappaport and others have found useful; but offers a more detailed method of study of such content than either Rappaport or Murray. The approach is eclectic. Most clinicians should find the

method of TAT analysis found here quite useful.

The author begins with an all-too-brief history of the development of the test, mentioning only vaguely its relation to other projective techniques and to the concept of mental testing in general. He then proceeds with a discussion of reliability and validity, largely in terms of statistical coefficients, derivation of which is left entirely to the reader's imagination or to his enterprise in looking up the references given. In a short chapter on administration, general instructions are given.

The scoring system suggested by Tomkins is admittedly cumbersome and time-consuming and will probably prove more useful as an instrument for research than as a practical clinical tool. The elements included in the system, however, undoubtedly constitute a helpful guide and should be very useful if kept in mind while working with the test, even though most clinicians will find it inexpedient to use the system formally. Among the concepts employed in the scoring system are: (1) ten vectors; (2) seventeen levels or planes of psychological function; (3) twelve conditions or states imposed on the subject; (4) qualifiers—more specific aspects of either vectors, levels or conditions, e.g., temporal characteristics, contingency, intensity, causality, et cetera. There is a distinct gap in the relationship between the scoring system and the interpretation, which seems not to depend to any great extent on quantitative findings.

The bulk of the book is devoted to the problem of interpretation and includes many helpful sample stories. The material is considered in relation to: (1) family and home relationships; (2) love, sex, and marital relationships; (3) social relationships; (4) work and vocational setting. One of the most valuable chapters is that devoted to "Level Analysis" in which the relation between the story and the story-teller is probed. E. B.

HODGKIN'S DISEASE AND ALLIED DISORDERS. By HENRY JACKSON, JR., A.B., M.D., Asst. Prof. of Medicine, Harvard Medical School; and FREDERIC PARKER, JR., A.B., M.D., Assoc. Prof. of Pathology, Harvard Medical School. Pp. 177; 14 plates. New York: Oxford University Press, 1947. Price, \$6.50.

THIS important and interesting monograph is based upon a combined clinical and pathological study made by the authors over many years. Much of the material brought together in this volume has appeared from time to time in several medical journals, but it has now been correlated and condensed and some new observations have been added.

The major portion of this treatise is devoted to a discussion of Hodgkin's disease, followed by shorter chapters on related conditions. Each chapter assumes the character of a brief original communication. Abbreviated case histories are used to illustrate the course of the disease, and excellent photographs represent adequately the pathological lesions.

The authors conclude, from their study of 259 cases of Hodgkin's disease, that the condition appears in 3 distinct forms or stages. These can be distinguished both clinically and pathologically. The first, termed by them Paragranuloma, is comparatively benign and is often localized for long periods to regional lymph nodes; the second, termed Granuloma, the common type, is much more serious for it is generalized and frequently involves the internal organs, being prone to affect the lungs, bones, spleen and intestinal tract, though it does not invade the nervous system; the third, termed Hodgkin's Sarcoma, is highly malignant and may invade any organ in the body including the nervous system. "Transitional forms of these three types of Hodgkin's disease occur, but it is essential for the understanding of the clinical features to recognize the existence of each." It has long been known that Hodgkin's disease may acquire the properties of an invasive tumor, but the conception set forth by the authors is in general novel.

They reiterate the statement that the presence of the Reed-Sternberg giant cells is always essential for the pathological diagnosis of Hodgkin's disease. They hold the belief, not generally current, that Hodgkin's disease arises in a single focus, usually but not always located in lymph nodes, whence it spreads or metastasizes to distant organs. This view is important in relation to therapy for it offers the possibility of complete cure in an occasional case, particularly of the paragranulomatous type.

Of the related conditions next considered, reticulum cell sarcoma is regarded as a distinct entity, different from Hodgkin's disease sarcoma and lymphosarcoma. It may occur as a primary tumor of bone, of which they have observed 25 cases. Early amputation of the extremity, followed by radiotherapy,

may be followed by recovery; this occurred in 6 of 11 of their patients. The view is expressed that lymphocytoma and lymphoblastoma arise exclusively in lymph nodes and usually acquire their serious nature only when leukemia or lymphosarcoma develops. Lymphosarcoma, of which they encountered 67 cases with 12 autopsies, is regarded as one of the rarest forms of "lymphoma"; for they restrict the term to those cases which present a single invasive and destructive tumor. Giant-Follicle Lymphoma tends frequently to undergo transformation into Hodgkin's sarcoma, lymphosarcoma or reticulum cell sarcoma. Of the authors' cases 36% developed lymphosarcoma. Plasmocytoma is considered particularly from the point of view of the extra osseous growths. The authors record 5 such cases in some of which intraosseous growths never appeared. Endothelioma receives little more than mention, since the authors have never encountered a case.

The monograph contains a wealth of valuable information based upon personal experience, and obtained from a wide knowledge of the literature. No effort has been made, however, to incorporate a comprehensive bibliography. References are given at the end of each section or chapter to those articles and treatises that have the most significant bearing on the subject under discussion. The book will become an essential text for all physicians and students interested in this field.

W. L.

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DR. KIRKBRIDE AND HIS MENTAL HOSPITAL. By EARL D. BOND, M.D., Director of Research, Institute of the Pennsylvania Hospital. Pp. 163; 7 ills. Phila.: J. B. Lippincott, 1947. Price, \$3.50.

THE life of Thomas Kirkbride, first Superintendent of the Pennsylvania Hospital for Nervous and Mental Diseases, is here presented in the light of his own times. The son of a rigid, parsimonious Quaker farmer, he became a doctor with the choice of specializing in surgery or psychiatry. His reasons for selecting psychiatry boiled down to settling his parents' peace of mind and knowing that his wife approved any plan of medical practice that would keep him close by. Out of such small beginnings Doctor Kirkbride headed a mental hospital that became an inspiration to countless numbers and started the Pennsylvania Hospital on its road to leadership in the management and housing of mental patients and in the organization of psychiatry. Doctor Kirkbride was one of the thirteen founders of the American Psychiatric

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association, later became president of the early inspirational and, as succinct evidence of his organization, he was followed in that same post of president by five other Pennsylvania Hospital psychiatrists. The author, who is unusually qualified to record the life and times of Doctor Kirkbride, writes this biography as though he wished to present Kirkbride's personality in its living, of Philadelphia and Philadelphia descriptions in Kirkbride's time are delightful. This historical and sociological presentation offers the reader true understanding and insight into the developing personality. Throughout, Doctor Bond compares Doctor Kirkbride's psychiatric ideals in the housing and care of the mentally ill with our so-called modern advances. The reader is bound to conclude that there is a long road ahead. Anyone interested in psychiatry, Philadelphia book colorful and significant.

Practitioner. B. M. P.

DERMATOLOGY IN GENERAL PRACTICE. By SIGMUND S. GREENBAUM, B.S., M.D., F.A. Grad. of Pennsylvania Grad. etc. In col-  
his book colorful and his medical

phology, Univ. of Medicine, etc., etc.,  
School of Medicine, etc., etc.,  
Laboration with: LESTER W. BURKET, M.D.,  
D.D.S.; S. GORDON CASTIGLIANO, B.S., M.D.,  
D., F.A.C.S.; WILLIAM T. JOHNSON, M.D. Pp.  
SAXNER and HERBERT W. WADE, M.D. Pp.  
891; 846 ill., 20 in color. Phila.: F. A.  
Davis, 1947. Price, \$12.00.

practitioner, the time to time major clinical, diagnostic, and therapeutic facts about a particular mass of material presents a large mass of material which one might encounter if it is not handled properly.

It is so presented that the information would be readily accessible to the general practitioner in general practice; but it is contained on dermatology which is a specialist subject. It is due largely to the arrangement of the text that it is difficult to ab-

ditioner. This is the topic in appropriate treatment of the given dermatosis, since the premises that a given dermatosis can be diagnosed as read up on the case would be way he can read up on the case would be under what diagnosis he might be considered. Granting this point, some

he knew that his patients' erythrocytes still have trouble as they may have erythematous areas under the microscope. A case (e.g., lupus erythematosus) discussed out of alphabetical order under hematology (e.g., tuberculous). A first reference for ready reference.

to the alphabetized text later. In the  
useful arrangement for  
be to place all the illustrations in  
probable cases.

at through the pictures, find a  
gnosis, and limit the search for  
material on a case to a few pages.  
In this major defect, there is much  
to date, and for the most part  
clear, concise language. The sec-  
few typographical errors. The sec-  
cancer, leprosy and oral diseases are  
essentially well done by a valuable  
presentation of pruritus is a puzzle about  
the physician who is puzzled about  
do next for a patient with itching.  
lar mention should be made of the  
in eczema; vitamins; antihistamine sub-  
s; the treatment of acne vulgaris; the  
amides; the diagnosis of ringworm; the  
s of penicillin in dermatology and the  
relationship of peripheral vascular disease in  
tonology. An example of the up-to-date  
material is the use of streptomycin in granulo-  
ingualae.

Other specific suggestions are: to add dif-  
ferential tables, e.g., on pigmentations; on the  
acute exanthemata, etc. The illustrations in  
the text, and if the present arrangement is  
maintained, should be as near their text de-  
scriptions as possible. Furthermore, closer  
editing would prevent duplication of illus-  
trations (figures 384 and 381 are identical,  
except for color).

— GROUP THERAPY. Edited  
by H. B. —

THE PRACTICE OF  
by S. R. SLAYSON, Director  
of Jewish Board of Guardians, New York  
Pp. 271. New York: Internat. Univ. Press,  
1948. Price, \$5.00.

There are 4 chapters on children and makes no demands. There are 4 chapters on children and makes no demands. There are 4 chapters on children and makes no demands.

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AMERICAN MEDICAL RESEARCH PAST AND PRESENT. By RICHARD H. SHRYOCK, Ph.D., Prof. of History and Lecturer in Medical History, Univ. of Pennsylvania. Preface by JOHN F. FULTON, M.D. Pp. 350. New York: Commonwealth Fund, 1947. Price, \$2.50.

ONE of a series of monographs published at the request of the Committee on Medicine and the Changing Order of the New York Academy of Medicine. The material is presented under the following headings: Formative Influences, Early Support of Research, 1860-1895, The Changing Economic and Social Background, The Era of Private Support, 1895-1940, Research Trends, Research Fields, Public Relations, Public Support, The Future.

The history of medical research in America, from its feeble beginnings in the middle of the 18th century to its present position of leadership, is traced in a most readable style. The book affords stimulating entertainment from start to finish and furnishes an excellent background for an unprejudiced appraisal of the present status of medical research in America.

This book should be read by everyone engaged in medical research in this country, if only to facilitate the visualization of his own field of endeavor in proper perspective. To all who are interested in the medical, social and economic development of America, the Reviewer heartily recommends this little volume.

D. C.

BENJAMIN SILLIMAN (1779-1864) PATHFINDER IN AMERICAN SCIENCE. By JOHN F. FULTON and ELIZABETH H. THOMSON. Pp. 294. New York: Henry Schuman, 1947. Price, \$4.00.

BENJAMIN SILLIMAN occupies an unusual place in the history of American science. Although his original contributions were of a minor character, he probably accomplished more than did any other person in disseminating scientific knowledge and enthusiasms on both the popular and professional levels. A graduate of Yale College, Silliman was appointed to the first professorship of chemistry there in 1801 while still quite innocent of scientific training. He proved to be just the man for the post, not only because of intellectual ability but also because his personal tact, integrity, and enthusiastic industry were just the qualities needed for establishing science in an educational world still dominated by the classical tradition. In this respect, he was also aided by an honest but tolerant piety, which served to overcome the fears which

science would otherwise have aroused at so orthodox a center as New Haven.

So equipped, Silliman prepared for his career by securing training in chemistry and medicine at the University of Pennsylvania, and by spending a stimulating year in Europe. Returning to Yale in 1806, he served there for half a century, guiding two generations of able students and founding scientific institutions which were of national as well as local importance. He was not only the first professor of chemistry at Yale, but the first to teach geology in the United States (1806). In 1810 he led in the founding of the Yale Medical School. Displaying a genius for organization and for raising what were then substantial funds, he secured for Yale collections in geology and in the fine arts. In 1818 he established the *American Journal of Science* ("Silliman's Journal"), which became a clearing house for the scientific interests of the nation. In 1846 he persuaded the College to set up the first courses in science independent of the Arts College, an arrangement which led later to the beginnings of the Sheffield Scientific School and to a Graduate School which gave the first American Ph.D. (1863).

While engaged in all these activities, Silliman also found time to serve as a consulting mining engineer and as a very successful popular lecturer. Although there was already a tendency to separate pure and applied science, and to isolate basic science from the public, Silliman was opposed to this by both temperament and conviction. Not a technical specialist, he valued science primarily as a means for economic progress and for popular enlightenment. In this respect, he may be viewed as one who preserved the scientific outlook of the preceding century while at the same time he did so much for the institutions of the future.

Dr. Fulton and Miss Thomson have based this biography on a thorough use of the great mass of Silliman papers, as well as on materials found in other collections. Their treatment is a sympathetic one, tempered by objectivity. The result is a most happy combination of careful scholarship and human interest, calculated to widen the horizon of any reader concerned with the development of the sciences in this country.

R. S.

ORAL VACCINES AND IMMUNIZATION BY OTHER UNUSUAL ROUTES. By DAVID THOMPSON, O.B.E., M.B., Ch.B., D.P.H., Director of the Pickett-Thomson Research Laboratory, ROBERT THOMPSON, M.B., Ch.B., Patho-

logist, St. Paul's Hospital, London, and JAMES TODD MORRISON, M.D., D.P.H. Pp. 329. Balt.: Williams & Wilkins, 1948. Price, \$11.00.

THIS book brings together in 1 volume the results of many researches on oral vaccines and attempts at immunization by other non-parenteral routes. The summaries of over 1000 research papers are given in chronological order, but at the end of most chapters the authors have attempted to sum up the evidence and to give just and unbiased conclusions. Part I contains general information on oral immunization. Part II gives data on the oral method of immunization against numerous infectious diseases; pollinoses, and poison ivy dermatitis; the use of staphylococcal, streptococcal, gonococcal, *B. coli* and *B. pyocyaneus* oral vaccines; the use of oral vaccines in certain animal diseases; and passive oral immunization with placental extracts and seroplasma. Part III is limited to the oral prophylaxis with toxins and toxin-antitoxin mixtures, and Part IV lists attempts at immunization by other unusual routes. All the references to the literature are listed alphabetically in the back of the book. There are also author and subject indices. Those interested in the subject of immunization will find this a useful volume. H. M.

#### INTRODUCTION TO THE HISTORY OF SCIENCE.

Vol. III (in 2 parts). *Science and Learning in the 14th Century*. By GEORGE SARTON, Associate in the History of Science, Carnegie Institution of Washington. Pp. 2154. Balt.: Williams & Wilkins, 1947, 1948. Price, \$20.00.

THIS really colossal undertaking has already resulted in 3 large books—Vol. 1 (839 pp. covering the period from Homer to Omar Khayyam) appearing in 1927, and Vol. 2 (1251 pp. covering the 12th and 13th centuries) appearing in 1931 in two books but with continuous pagination and a single index. Now after 17 years, the 14th century is covered by Vol. 3, divided in the same way as Vol. 2. Thus one scholar, working for some 36 years, has brought to fruition his vast and unique plan of bringing into one work the scientific and cultural record of the civilization of the world up to the time of the Renaissance. Truly a Gargantuan "Introduction"!

The author's original purpose, "to explain the development of science across the ages and around the earth," is pursued in these two books on the lines laid down in the earlier two volumes. As this plan is complicated, he facilitates their use by explaining

their construction. Each deals with one half of the 14th century and the two are symmetrical; that is, each has 14 chapters, the first of which is a synthesis of the other 13. These 13, each of which has the same title as its vis à vis in the other book, are on such topics as Philosophical and Cultural Background, Medicine (these 2 being the largest), Education, Chemistry, and so on. They are packed with countless factual items, impossible for extended consecutive reading, nor are they intended for such. The first chapter of each part, on the other hand, each consisting of more than 300 pages and subdivided into the same sections as are the subsequent 13 chapters, amalgamates into a scholarly readable story the knowledge of the period in each field of endeavor. These 2 survey chapters are obviously the author's favorite part of the work, to which the rest play subordinate if necessary supporting roles. From these and from his Introductory Chapter, readers will learn much about the intellectual activities of the 14th century and the unifying bonds between different countries, a special emphasis being given to the contributions of Eastern thought.

The General Index requires 373 large double columned pages, and even so is followed by shorter indices in Greek, Chinese and Japanese characters. In true Sartonian manner, the General Index is described as not only "relatively complete" for Vol. 3, but also "a very rudimentary repetition" of the indexes of the first two volumes. As has been noted elsewhere, the extensive index and bibliographical notes make the work of very considerable use as a dictionary and a bibliography of the period, but these are by-products and should not detract from its greater role as "an integration of the intellectual doings" of the scholars and scientists of the 14th century.

Even to erudite scholars, and with due allowance for assistance received, the author's encyclopedic knowledge must seem prodigious. One wonders who could write an adequate critical review of these volumes except Dr. Sarton himself. Let us hope with him that, even if he has now concluded the undertaking 5 centuries short of his original goal, he may be found to have pointed the way for others to carry on the task. E. K.

**PATHOLOGY OF TUMOURS.** By R. A. WILLIS. D. Sc., M.D., F.R.C.P., Prof. of Human and Comparative Pathology, Royal College of Surgeons, London. Pp. 1050; 500 ills. St. Louis: C. V. Mosby, 1948. Price, \$20.00. PROFESSOR Willis' previous book, "The

"Spread of Tumors in the Human Body" is rightly regarded as one of the significant contributions to the literature on oncology. The present larger and more comprehensive work deals with all aspects of neoplasia and neoplastic diseases, and is, as the author states, the outcome of his special interests in tumors during 20 years as a hospital pathologist.

The book is addressed primarily to pathologists, research workers and senior students, but Professor Willis expresses the hope that "clinicians also may find it useful and even elementary students may find it intelligible." This hope is amply justified. The book gives not only a well balanced and readable account of present day knowledge, but also constitutes an invaluable record of the authors' own observations and conclusions. Many brief reports of personally studied cases are introduced as examples; on controversial matters, while indicating that they are controversial, Professor Willis has plainly stated his own present opinion; the figures, of which there are 500, are all from material which he has studied personally.

The first part of the work (about 200 pages) deals with general aspects of tumors, such as definition, classification and nomenclature, the proper meaning of "innocence and malignancy," the experimental production, statistical study, mode of origin, structure and growth, spread, and modern hypotheses as to the nature of tumors. The author's conviction that much has yet to be learned from the comparative pathology of tumors is reflected not only by a separate chapter on tumors in animals, but by sections in the chapters which are devoted to tumors in the different organs. Part I ends with a recapitulation of the subjects discussed and the conclusions reached.

Part II of the work is concerned with what is sometimes referred to as special oncology: a systematic consideration, first of the epithelial tumors, malignant or benign (somewhat over 400 pages); then of the mesenchymal tumors, including those arising from lymphoid and other haemopoietic tissues (approximately 150 pages); the tumors of neural tissues (approximately 100 pages), and finally sundry special classes of tumors such as melanomas, embryonic tumors of viscera, teratomas and chorioepitheliomas (approximately 100 pages). The reference lists are carefully chosen; as the author says, he has preferred to base his discussion on what he has read himself; many of the references are annotated, as "a valuable review of the physical and chemical properties of tumor cells, including a discussion of their invasiveness." The text is well printed; the index is good. The book is warmly re-

commended. The pathologist will find in it much of interest, for it expresses clearly and frankly the opinion of a distinguished fellow pathologist; the student of medicine will find it a good guide to a difficult subject, and the clinician an excellent and readable work of reference.

B. L.

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HEART. By ALDO A. LUISADA, Instructor in Physiology and Pharmacology, Tufts College Medical School. Pp. 653; 352 ills. Balt.: Williams & Wilkins, 1948. Price, \$10.00.

THE author stresses the physiologic basis for normal and abnormal functions of the heart and circulation. The characteristics of and reasons for symptoms and physical signs are well demonstrated by graphic methods. The separation of chapters on the basis of an anatomical rather than an etiologic classification is admirably suited for this purpose. The use of mechanical aids to diagnosis, especially phonocardiography, is extensively illustrated. Rare and unusual forms of heart disease are covered scantily or not at all. No attempt is made to discuss advanced electrocardiography. This book is recommended especially for its clear descriptions of normal and abnormal cardiovascular physiology and the use of technical aids in understanding these problems.

C. K.

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A HISTORY OF THE HEART AND THE CIRCULATION. By FREDRICK A. WILLIUS, M.D., M.S., Prof. of Medicine, Mayo Foundation, and THOMAS J. DRY, M.S., Assoc. Prof. of Medicine, Mayo Foundation. Pp. 456; illustrated. Phila.: W. B. Saunders, 1948. Price, \$8.00.

THE numerous books on historical and cultural aspects of medicine that have appeared since the War give a good indication of the interest that the medically inclined public—at least in publishers' opinions—has in this field. Anthologies and systematic treatises, both general and in special fields, present ever increasing opportunity for contact with the concepts, achievements and personalities of our past.

The present volume, one of the best in a field in which it has several predecessors, offers its material in 3 main divisions. The first and longest part (268 pp.) presents the story in 8 chronological divisions that increase in length from the earliest. Antiquity (23 pp.) to the latest, the First Quarter of the Twentieth Century (45 pp.). The second section gives in more detail 20 arbitrarily selected "Special Biographies" (ranging from Hippocrates to Sir Thomas Lewis) of men who have already appeared in the earlier part.



The third section, "The Chronologic Presentation of Data According to Subject," presents 18 tabulated chronologies of such subjects as Aneurysm, The Pulse, the Anatomy, the Physiology, the Therapy of the Heart and Circulation, Milestones in Medical Education (not restricted to the special field of the heart) and so on. This unusual arrangement, in addition to requiring considerable repetition, produces many breaks in continuity. Osler, for instance, is given 2 pages in the general history, then 10 in the biographical section, with mention in several of the chronological lists. Resultant inconveniences are minimized, however, by good indices.

Among the many illustrations, there is a refreshingly high percentage, especially in recent times, of newcomers to historical texts. The welcome emphasis on the modern here and throughout the volume, not only results in an allocation of text space more proportional to the actual progress made but also provides all the more information that is not to be found in out of print histories. It is perhaps needless to add that the work is not a History in the professional historian's sense, and it is probably not meant to be, but it does appeal to the Reviewer as an adequate and entertaining account of the progress of one of the most important fields of human medicine.

E. K.

**NO RETREAT FROM REASON AND OTHER ESSAYS.** By ALFRED E. COHN. Pp. 279. New York: Harcourt Brace, 1948. Price, \$3.50.

The author of this group of essays has been consistently a vigorous advocate of the intellectual attitude toward life. His faith is based upon the progressive use of intelligence to solve man's problems and to achieve happiness and the good life.

The essay which names the collection presents an optimistic appraisal of our opportunity in the confused and turbulent world we find about us. Its calm and reasoned approach is entirely wholesome. Several of the essays deal with the interaction of the method of science and the achievements of the arts. The analysis of this interaction has long been a favorite field of inquiry for the author and he has contributed significantly to it. Three essays are biographical appraisals of men of medicine; two of them men of recent years; the other, Harvey. A chapter entitled "On Retiring" is a delightfully humorous interlude, nevertheless permeated with thought-provoking philosophy.

J. A.

**THE METABOLIC BRAIN DISEASES AND THEIR TREATMENT IN MILITARY AND CIVILIAN**

**PRACTICE.** By G. TAYLEUR STOCKINGS, M.B., Late Deputy Medical Superintendent, City Mental Hospital, Birmingham, England. Pp. 262; 3 ills. Balt.: Williams & Wilkins, 1947. Price, \$4.50.

This book is a re-interpretation of the schizophrenic, delusional, and affective psychoses, using a new, simpler terminology and classification, which is based on the results of the latest research in neurophysiology and psychiatry, plus 5 years extensive experience with insulin and electroshock ("neurometabolic") therapy in treating mental casualties of World War II. The author presents a remarkably unified and cogent concept of the psychoses as diseases of brain metabolism (encephalopathies) affecting either one or both of the 2 fuels of the brain cells—oxygen and glucose. The largest portion of the book is then devoted to a very thorough discussion, using this concept, of these disorders, presented much in the same way that a textbook in internal medicine would describe pneumonia, giving etiology, diagnosis, course, prognosis, and therapy, with an explanation of how the therapy works. By thus tying mental symptoms to disorders of biochemistry and the physiology of the brain, he brings the pathophysiology of psychoses into line with such psychosomatic diseases as essential hypertension, and establishes their treatment as rational and not empirical.

This is an extraordinary and possibly revolutionary book, which may become a milestone in psychiatry. It deserves a wide audience.

J. S.

**MEDICAL RESEARCH IN WAR.** Report of the MEDICAL RESEARCH COUNCIL for 1939-45. Pp. 455. London: His Majesty's Stationery Office, 1947. Price 7/6 net.

This report, covering the War Period is the first to be published by the Council in 8 years. So widespread are the ramifications of Council promoted activities that a fair picture emerges of British medical research in war time. The work was carried out in the National Institute for Medical Research or in the Council's 21 External Research Establishments or through grants to individuals, and Fellowships. It covered such broad fields as Wounds and War Injuries, War Diseases, Therapeutics (including penicillin), Nutrition in War Time, Personnel, Research, Health in Industry, Preventive Medicine, Laboratory and Clinical Studies in the various specialties, Cell Growth, Genetics, Radiant Energy.

The excellent record of this government created body since its incorporation in 1920, and of its predecessor The Medical Research

Committee, should be of special interest to the American medical profession in these days of coordinated research and increasing governmental participation.

E. K.

**EXPERIMENTAL AIR-BORNE INFECTION.** By THEODOR ROSEBURY, with the co-authorship of the staff of the Laboratories of Camp Detrick, Md. Pp. 222; 40 figs. Balt.: Williams & Wilkins, 1947. Price, \$4.00.

This first Microbiological Monograph of the Society of American Bacteriologists presents results of investigations of experimental air-borne disease released by the Biological Warfare Service. Between December 1943 and October 1945 Dr. Rosebury with 11 co-authors and 16 mentioned assistants conducted investigations on Air-Borne Infection at Camp Detrick, Maryland, forecast by his report printed a few months ago in the *Journal of Immunology*. Disease was induced in small animals inhaling droplet nuclei aerosols of *Brucella suis*, Psittacosis virus (Borg), Psittacosis virus (6BC), *Malleomyces pseudomallei*, *Malleomyces mallei*, Meningopneumonitis virus (Cal 10), and *Pasteurella tularensis*; the report does not indicate whether the list is complete but states, "work with infective agents was begun 21 March, 1945 and continued until shortly after the end of the war." These protocols occupy one-tenth of the volume.

The remaining nine-tenths of the book records the procurement of equipment and secret training for a study of experimental air-borne disease. The first part describes elaboration of apparatus for safe exposure of animals to aerosol suspensions of virulent organisms in droplet nuclei. The second describes certain selected atomizers for producing infective aerosol clouds. The third part discusses their modification of the Greenburg dust impinger for bacterial sampling. Since alteration of critical dimensions sacrifices impinging efficiency, the authors state "that the sampler operates as a bubbler rather than as an impinger in the strict sense"; bubblers are much less efficient collectors of droplet nuclei than impingers. Yet the violence of this type of impinger may, by destroying delicate organisms, as the authors suggest, perhaps account for the small lethal dosage (one-third) obtained by British investigators of Biological Warfare; quantitative precision is illusive.

Nevertheless the mortality patterns parallel previous results on air-borne influenza and streptococcal infection of mice in that geometrical increases in dosage tend to yield arithmetic increases in mortality, and the work provides valuable new evidence of the

vulnerability of animals to inhaled droplet nuclei infection.

W. W.

**RHEUMATISM AND SOFT TISSUE INJURIES.** By JAMES CYRIAX, M.D., B.Ch. (Cantab.), Physician-In-Charge, Physiotherapy Dept., St. Thomas's Hospital, London. Pp. 410; 107 ills. New York: P. B. Hoeber, 1947. Price, \$9.50.

ACTUALLY a work on physical therapy, particularly on massage and manipulative techniques, this book gives an excellent description of the physical management of various muscle and joint conditions. "Treatment by movement has been substituted (for rest) for many traumatic and rheumatic lesions in the course of the present century. Movement may be applied in various ways . . . active and resisted exercise, forced movement, and deep massage."

The sections discussing muscular spasm and fibrotic nodules are well thought out. The plates and figures are well done and interesting, although in many cases the techniques illustrated are dubious in value or even dangerous—such as manipulation of the cervical spine for rheumatoid spondylitis.

Why treatment of conditions of the alimentary tract, of herpes zoster and of retraction of the nipple should be included in this work is something of a mystery. Many of the terms used are confusing and the conditions described are somewhat garbled, particularly the descriptions of functional conditions, such as "psychogenic spasms," "sciatic scoliosis," "capsulitis," etc. The book shows little organization from the standpoint of disease entities, but is loosely organized from the standpoint of parts involved and treatments for each area. The section on rheumatoid arthritis is rather confusing in its arrangement, and the symptomatology and diagnostic criteria are sketchy and incomplete.

It is felt that this book would be of limited value to a general practitioner or an internist, because of its sketchy method of describing the diseases of the joints and muscles, and because of the emphasis on manipulative techniques which should be carried out only by an expert in physical therapy, if at all. It can be taken, however, as a reference work for massage and manipulative techniques, and for diagnostic criteria for the more obscure soft tissue injuries.

J. H.

**SOURCE BOOK OF ORTHOPAEDICS.** By EDGAR M. BICK, M.D., F.A.C.S., Orthopedic Surgeon, Mt. Sinai Hospital, New York. 2d ed. Pp. 540; 31 ills. Balt.: Williams & Wilkins, 1948. Price, \$8.00.

Dr. BICK after 10 years has brought out another edition of his *Source Book* which is an enlarged and much more valuable history of the development of Orthopaedic Surgery. This is a most interesting book, weaving the advances of the specialty around the personalities connected with the various affections of bones and joints, and integrating into it the more recent developments. This broad concept has been difficult to crystallize into book form, as the author frankly admits; but Dr. Bick is to be congratulated upon producing an interesting history of orthopedic surgery. His extensive bibliography attests to his wide reading and preparation in making this edition even more valuable than the first.

P. C.

**MEDICOLEGAL PROBLEMS.** Edited by SAMUEL A. LEVINSON, M.D., Ph.D., Univ. of Illinois College of Medicine, for the Committees of the Institute of Medicine and the Chicago Bar Association. Pp. 255; 6 ills. Phila.: J. B. Lippincott, 1948. Price, \$5.00.

THE first aim of this book is to provide both medical and legal professions with an understanding of the viewpoints of the other, so that judicial review may be honest and fair. Secondly, it brings together both professions so that conditions requiring legislative action may be undertaken. And lastly, the legal liability of the physician in various situations is clarified.

The phases covered are: the medical witness and the Minnesota plan; artificial insemination; medicolegal pathology, sterility operations; trauma and tumors; scientific tests in evidence. Each problem is covered medically, legally, and the discussion following each presentation is included. The treatment of each phase is satisfactory and enlightening. It is of importance for the physician to realize the conservatism of the bench, and the difficulty (in some states) of establishing medical tests and facts as incontrovertible evidence.

G. R.

**DISABILITY EVALUATION.** By EARL D. McBRIDE, B.S.M.D., F.A.C.S., Diplomate American Board Orthopedic Surgery. 4th ed. Pp. 667; 400 ills. Phila.: J. B. Lippincott, 1948. Price, \$12.00.

THE fact that this is the 4th edition of this extensive work is its best commentary. There is no other book in English that covers the subject in such a complete and comprehensive way.

One could easily find fault with minor matters, such as the treatment of the hysterics, the neuroses and malingering, and ob-

ject that from the psychoneurotic aspect of injuries the subject is treated from the standpoint of the employer.

The traumatic neurosis should be considered as a definite entity, as an actual clinical disease process, if one would be fair to the plaintiff. If this were done, it would add definitely to the value of the book. It is not fair to pick out such a highly technical and specialized subject as nervous diseases and psychiatry and more particularly the functional group when this needs a special volume for its interpretation. The author's composite schedule of approximate evaluations for partial permanent disability, which has been given a prominent position in the book, will prove of great value in compensation cases. The large number of line and photographic illustrations, all of them particularly well done, add tremendously to the book's value.

It should be in the hands of both doctors and lawyers interested in workmen's compensation and transportation damage suits. It will also be of value to the ordinary physician who is asked to testify in damage and compensation cases. It is a splendid book of reference.

D. McC.

**PSYCHOBIOLOGY AND PSYCHIATRY.** By WENDELL MUNCIE, M.D., Assoc. Prof. of Psychiatry, Johns Hopkins Univ. 2d ed. Pp. 620; 70 ills. St. Louis: C. V. Mosby, 1948. Price, \$9.00.

THIS new edition of this valuable presentation of the teachings of Adolf Meyer, seen through the clinical experiences of Dr. Muncie, omits many of the blank spaces of the 1st edition but adds many new facts.

The 3 parts of the book consider the normal chiefly through personality studies of medical students, the abnormal with chapters on each mental disease or defect, and treatment in general and for particular abnormal reactions.

As Adolf Meyer's terms have not been adopted by others, they do not add much to the reader's comfort. But the basic concepts are so original, sweeping and dignified that they deserve a place in any psychiatrist's thinking. And their spirit is indicated in a quotation from William James, "Experience exceeds logic, overflows and surrounds it".

E. B.

#### NEW BOOKS

*Advances in Biological and Medical Physics.* Vol. I. Edited by JOHN H. LAWRENCE and J. G. HAMILTON, Univ. of California. Pp. 484. Illustrated. New York: Academic Press, 1948. Price, \$8.60.

*Cancer Manual. Standards for the Diagnosis and Treatment of Cancer.* By the CANCER COMMITTEE of the Iowa State Medical Society. Pp. 160. Iowa City: Athens Press, 1948. Price, \$1.00.

*Hetero-specific Alteration Therapy.* By S. NUKADA, M.D., Ph.D., and C. RYU, M.D., Nukada Institute and Sanatorium. Pp. 80; 5 ills. Tokyo, Japan: The Japan Medical Publications Co., 1948. No price given.

*Diagnosis in Gynaecology.* By JAMES V. RICCI, M.D., Clinical Prof. of Gynaecology and Obstetrics, New York Medical College. Pp. 259. Phila.: Blakiston, 1948. Price, \$4.50.

*Rural Health and Medical Care.* By FREDERICK D. MOTT, M.D., and MILTON I. ROEMER, M.D., M.P.H. Pp. 608. New York: McGraw-Hill, 1948. Price, \$6.50.

*Vitamine und Vitamintherapie.* Von DR. MED. EMIL ABERHALDEN, Univ. Zurich. Pp. 408; 42 ills. Bern, Switzerland: Hans Huber, 1948. Price, Fr. 28.

*The Engaged Couple Has a Right to Know.* By ABNER I. WEISMAN, M.D. Pp. 256. New York: Renbayle House, 1948. Price, \$3.00.

*Pharmacology and Therapeutics in Nursing.* By MARION SYLVESTER DOOLEY, M.D., and JOSEPHINE RAPPAPORT, R.N., B.S. Pp. 444; 26 ills. New York: McGraw-Hill, 1948. Price, \$3.75.

*Corazon Pulmonar e Insuficiencia Coronaria.* Por el DR. JUAN GOVEA, de la Facultad de Medicina de Paris. Pp. 178; 70 ills. Havana, Cuba: M. V. Fresneda, 1948. No price given.

*The Healthy Hunzas.* By J. I. RODALE. Pp. 263; 16 ills. Emmaus, Pa.: Rodale Press, 1948. Price, \$2.75.

The food and farming habits of a people dwelling on the northwestern border of India.

*Treatment of Heart Disease.* By WILLIAM A. BRAMS, M.S., M.D., Ph.D., Assoc. Prof. of Medicine, Northwestern Univ. Pp. 195; 11 ills. Phila.: W. B. Saunders, 1948. Price, \$3.50.

*Chemistry in Nursing.* By RAYMOND E. NEAL, Assoc. Prof. of Chemistry, Simmons College. Pp. 564. New York: McGraw-Hill, 1948. Price, \$4.00.

*Advances in Protein Chemistry.* Vol. IV. Edited by M. L. ANSON, Continental Foods, Inc., and JOHN T. EDSALL, Harvard Medi-

cal School. Pp. 575; 13 ills. New York: Academic Press, 1948. Price, \$8.50.

*An Introduction to the History of Dentistry.* By BERNHARD WOLF WEINBERGER, D.D.S. In 2 vols. Pp. 514 and 408; 177 and 136 ills. St. Louis: C. V. Mosby, 1948. Price, \$20.00.

## NEW EDITIONS

*Human Neuroanatomy.* By OLIVER S. STRONG and ADOLPH ELWYN, College of Physicians and Surgeons, Columbia Univ. 2d ed. Pp. 442; 336 ills. Balt.: Williams & Wilkins, 1948. Price, \$6.00.

WE welcome a new edition of *Human Neuroanatomy*, by Professors Strong and Elwyn, for it is one of the best and most ably written books in a large field on this subject. The first edition was developed from chapters on the nervous system which, for years, had been incorporated in Bailey's *Histology*. (It was reviewed in this Journal 206, 809, 1943.) The 2d edition has been improved by addition of one new chapter and enlargement of another.

The new Chapter X, on Segmental and Peripheral Innervation, employs several new illustrations, principally from an excellent small clinical book by Haymaker and Woodhall. The expansion of Chapter XXI is notable. The account of the blood supply of the brain, especially the blood vessels of the basal ganglia and internal capsule, is splendid.

This book is for the advanced or more serious student of neurology. Some aspects of it are too heavy for the neophyte. This is not an adverse criticism, but rather one of the inadequate time available for study of neuroanatomy in many medical schools. W. W.

## HOSPITAL CARE OF NEUROSURGICAL PATIENTS.

By WALLACE D. HAMBY, M.D., F.A.C.S., Prof. of Neurology and Neurologic Surgery, Univ. of Buffalo School of Medicine. Springfield, Ill.: Charles C Thomas, 1948. 2d ed. Pp. 156, 30 figs. Price, \$3.00.

THIS is a very satisfactory little book. It reviews briefly and concisely, the major types of cases seen on a neurosurgical service. The preoperative care and the special tests to be employed in each group of cases are carefully outlined. The major postoperative complications together with the proper method of handling them are well described. The format and appearance of the book is pleasing. Residents, internes and nurses connected with a neurosurgical service can read this book with profit.

F. G.

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